The association between bone metabolism markers and hypertension in osteoporotic patients

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Abstract

Background.

Hypertension may be related to osteoporosis through increasing parathyroid hormone (PTH) and catecholamines which promote osteoclast differentiation and bone resorption. There are previous studies on the relationship between hypertension and bone turnover markers but they are still unclear. The aim of the case study is to examine the association between hypertension and the level of bone metabolism markers in osteoporotic patients.

Methods.

A cross-sectional study of 518 subjects was done to see the association between hypertension and the level of osteocalcin (OC), bone-specific alkaline phosphatase (B-ALP), Tartrate-resistant acid phosphatase (TRAP.5B) and 25-hydroxy vitamin D(25-OHD). All of the subjects were divided into two groups for analyzation: with or without hypertension. Subgroup analysis was based on sex for further analysis. The associations were assessed by the univariate analysis and multivariate regression analysis. Potential confounders were also adjusted for multivariate regression analysis.

Results.

There were 243(46.9%) osteoporosis patients with hypertension. Both univariate and multivariate analysis have suggested that lower OC and 25-OHD levels were associated with hypertension. The potential confounders-adjusted OC level was significantly lower in hypertensive female group than that in the female without hypertension group(β= -0.20, 95%*CI*= -0.37 to -0.03, *P* = 0.02 in final adjust model). The potential confounders-adjusted 25-OHD level was significantly lower in hypertensive male group than that in male without hypertension group (β= -0.34, 95%*CI*= -0.58 to -0.10, *P* = 0.01 in final adjust model). The B-ALP and TRACP.5B levels were positively associated with hypertension in univariate or multivariate analysis. In subgroup analysis, there was a consistent correlation between hypertension and B-ALP level in females and male subjects, but there was no consistent correlation between consistent correlation and TRACP.5B. However, all the correlations had no statistical significance for the B-ALP and TRACP.5B.

Conclusions.

In this study, hypertension was associated with low level of OC in female group and hypertension was associated with low level of 25-OHD level in male which show that OC and 25-OHD may play a role in bone loss.

Background

Osteoporosis is a metabolic bone disease which is characterized by decrease of bone mass as well as degeneration of bone microstructure. Osteoporosis is prone to fracture due to increasing bone fragility[1]. Also, the incidence of osteoporosis has a direct relationship with the age of the patient. With the aging population in China, osteoporosis has become an important public health problem in China. However, the etiology of primary osteoporosis is complicated and has yet fully be understood. Furthermore, hypertension is a major cause of cardiovascular disease and the prevalence of hypertension has significantly increased during the recent decades in China[2]. Many studies evaluating a relationship between hypertension and osteoporosis have been published in the past. Overall, there are significant evidence that indicate that high blood pressure is associated with increased bone loss. The association between high blood pressure and boneloss may have contributed to the risk of fractures[3, 4].

Hypertension is thought to be linked to bone health through chronic elevation in the levels of PTH and catecholamines (including adrenaline and angiotensin II).In addition, hypertensive patients have decreased intestinal absorption, increased urinary calcium excretion, and decreased plasma vitamin D concentrations which promote PTH continuous secretion[5]. Also, sustained elevation of PTH contribute to bone resorption by increasing osteoclast differentiation[6]. Activation of the renin-angiotensin system in hypertensive mice accelerates bone resorption, induces high bone turnover osteoporosis[7] and it may eventually increase the riskof fragile fractures.

Although bone turnover was regulated by hypertension has been elaborated in animal model, there are little amount of clinical data indicating whether hypertension independently influences bone turnover. OC and B-ALP were commonly used to evaluate bone formation and 25-OHD was considered as bone mineralization regulator. In addition, TRACP has properties indicating that it can be a good marker of bone resorption and osteoclast activity. The determination of TRACP, especially TRACP-5b in serum, can help to understand physiological conditions and various bone metabolism under pathological conditions. Previous studieson the relationship between blood pressure and bone formation have demonstrated conflicting conclusions which is that OC was shown inversely or positively related to high blood pressure[8–10]. Higher blood pressure was also significantly correlated with increased ALP, but there were few studies showing the correlation between B-ALP and hypertension. There was a consistent result that hypertension patients had vitamin D insufficiency which was involved in the pathogenesis of bone loss. However, as far to our knowledge, there was no clinical data on estimation of the serum TRACP.5B in hypertensive patients. In order to furthe-r elucidate the role of hypertension in bone metabolism, the purpose of this st-udy is to examine the association between hypertension and bone metabolism markers in osteoporotic patients.

Methods

Study Participants

Osteoporotic patients were admitted to orthopedics department of the Affiliated Hospital of Guangdong Medical University in China for fragility fracture from January 2013 to January 2016. A total of 518 patients with osteoporosis were enrolled in this study after rigorous diagnosis and exclusion criteria.All patients orally agreed to participate in this study. The project was performed in accordance with the principles of the Declaration of Helsinki and it is approved through the Ethics Committee of the Affiliated Hospital of Guangdong Medical University(Approval NO. PJ2012026).

Diagnosis and Exclusion Criteria

All of the patients were diagnosed with osteoporosis and admitted to our hospital for the first time. In short, each eligible patient met the following inclusion criteria: (1)his or her discharge diagnose was primary osteoporosis which was confirmed and signed by the chief physician and attending physician; (2)age ≥ 50 years old. Subjects were excluded if they: (1)were below 50 years old; (2)were the premenopausal female patients; (3)no sure that patients newly diagnosed with osteoporosis; (4)were caused by other causes such as accident, trauma, tumour; (5)were the patients who had a history of fragile fracture; (6)had severe cardiovascular and cerebrovascular diseases, severe liver and kidney dysfunction, severe infection; (7)receiving glucocorticoids treatment.

The case study was hospital-based cross-sectional study and the clinical data were extracted from the medical records. Information including the age, gender, occupation, fragile fracture, related medical history and anti-hypertentive medication history were collected for each patient. In addition, the diagnostic criteria for hypertension was based on the 1999 World Health Organization-International Society of Hypertension Guidelines in which the hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or receiving an anti-hypertensive treatment[20]. All the biochemical examinations were completed in the clinical lab of the Affiliated Hospital of Guangdong Medical University. Normal bone metabolism markers levels ranges were shown in Table 1. Furthermore, all clinical records of the eligible cases were manually proofread by another researcher in a blinded fashion.

Statistical analysis

Empower (R)(www.empowerstats.com, X&Y solutions, Inc Boston, MA) and R (http://www.R-project.org) were applied to all statistical analyses in the research. Data were presented as mean ± SD, proportions or median(range). Subjects were divided into non-hypertensive and hypertensive groups. The correlations between hypertension and bone metabolism markers were assessed in both univariate and multivariate analysis by using linear regression models. The potential covariates were screened by being adjusted through generalized linear models. The screening criteria included risk factors producing > 10% change in the regression coefficient after introduction into the basic model. In order to obtain a more normal distribution, the Log of bone markers was used for calculation. All *p*-value of less than 0.05(two-tailed) were defined as statistical significance.

Results

Clinical Characteristics of Study Groups

The baseline characteristics of the study participants were presented in Table 1. The mean age of the total subjects was 75.15 ± 10.24 years. 71.11% of the participants were females. There were 243(46.9%) osteoporosis patients with hypertension. Diseases of respiratory system among the participants included chronic obstructive pulmonary disease, chronic bronchitis.

Table 1
Characteristics of the osteoporotic patients

Characteristic	Without-hypertension	Hypertension	*P*-value
Age(years)	73.59 ± 10.72	77.26 ± 9.16	0.001
Sex(female, %)	202 (73.45%)	168 (69.14%)	0.27
BMI(Kg/m^2)	22.78 ± 4.60	23.12 ± 4.54	0.40
Occupation			0.002
Light physical labor	90 (32.73%)	104 (42.80%)	
Moderate physical labor	83 (30.18%)	83 (34.16%)	
Hard physical labor	102 (37.09%)	56 (23.05%)	
Total Ca(mmol/L)*	2.20 (1.50–3.40)	2.19 (1.86–3.60)	0.79
OC(ng/ml)*	19.86 (1.93–109.40)	17.51 (2.72–64.86)	0.02
25-OHD(ng/ml)*	22.10 (2.73-70.00)	20.48 (3.00-55.34)	0.10
B-ALP(ug/L)*	0.56 (0.10–2.43)	0.58 (0.10–1.39)	0.51
TRACP.5B()*	39.87 (3.80-274.60)	42.21 (9.42–159.1)	0.72
Comorbidities			
Type 2 diabetes	24 (8.73%)	35 (14.40%)	0.04
Cerebral infarction	9 (3.27%)	19 (7.82%)	0.02
Coronary heart disease	16 (5.82%)	34 (13.99%)	0.002
Disease of respiratory system	20 (7.27%)	12 (4.94%)	0.21
Chronic renal insufficiency	5 (1.82%)	6 (2.47%)	0.61
Osteoarthritis	25 (9.09%)	26 (10.70%)	0.54
Anti-hypertension drugs used			0.001
No	274 (99.64%)	192 (79.01%)	
Yes	1 (0.36%)	51 (20.99%)	

* Median(range); Anti-hypertension drugs including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, Beta-blockers, Calcium channel blockers and Loop diuretics

Univariate Regression for the relationship between hypertension and bone metabolism markers

Table 2 showed the Univariate analysis results of the relationship between hypertension and four variables which include the OC Log2 transform, B-ALP Log2 transform, 25-OHD Log2 transform, and TRAP.5B Log2 transform. In this univariate analysis, there were no variables being adjusted. In the hypertensive groups, the levels of OC decreased by 0.12 units (95% CI: -0.26 to 0.02, P = 0.09). The levels of B-ALP in the hypertensive group increased by 0.07 Unit (95% CI: -0.26 to 0.40, P = 0.68). As for the TRAP.5B, in the hypertensive group, the level was increased by 0.03 Unit (95% CI: -0.29 to 0.36, P = 0.84). For 25-OHD level in the hypertensive group, the level was decreased by 0.11 (95% CI: − .24 to 0.01, P = 0.06).

Table 2
Univariate Regression for the relationship between hypertension and bone metabolism markers(β, 95%CI, P value)

	OC **log2 transform**	**B- ALP** **log2 transform**	**25-OHD** **log2 transform**	**TRACP.5B** **log2 transform**
Without-hypertension	Reference	Reference	Reference	Reference
With-hypertension	-0.12 (-0.26, 0.02) 0.09	0.07 (-0.26, 0.40) 0.68	-0.11 (-0.24, 0.01) 0.06	0.03 (-0.29, 0.36) 0.84
Adjust: None				

Multivariate Regression for the relationship between hypertension and OC level

Table 3 detailed the results of univariate and multivariate analysis for the relationship between hypertension and OC Log2 transform. Adjust I model shows the relationship between hypertension and OC when the basic covariate (year) was adjusted. The levels of OC decreased by 0.2 unit for hypertensive females (95% CI: -0.39 to -0.07, P = 0.004), and 0.16 unit for total subjects (95% CI: -0.30 to -0.02, P = 0.02). After adjusting for the variables of year, anti-cardiovascular disease drugs used, type 2 diabetes, and cardiovascular disease for adjusted II model, the result of multivariate analysis suggested that lower OC level remained significantly associated with hypertension in female subject (β= -0.2, 95% CI: -0.37 to -0.03, P = 0.02). The correlation in the total subjects had no statistical significance(β= -0.11, 95% CI: -0.26 to 0.03, P = 0.13). In adjust I model and Adjust II model, men in the hypertensive group showed higher serum OC level compared with those in the non-hypertensive group. but there was no statistical significance.

Table 3. Multivariate Regression for the relationship between hypertension and the OC level

(β, 95%CI, P value)

	hypertension	male	female	total
Adjust	No	Reference	Reference	Reference
	Yes	0.00 (-0.28, 0.29) 0.98	-0.23 (-0.39, -0.07) 0.004	-0.16 (-0.30, -0.02) 0.02
Adjust	No	Reference	Reference	Reference
	Yes	0.09 (-0.22, 0.39) 0.57	-0.20 (-0.37, -0.03) 0.02	-0.11 (-0.26, 0.03) 0.13

Adjust I model adjust for: Year. Adjust II model adjust for Year, Anti-hypertension drugs used, type 2 diabetes, Coronary heart disease

Multivariate Regression for the relationship between hypertension and B-ALP level

Table 4 showed the results of multivariate analysis for the relationship between hypertension and B-ALP Log2 transform. Adjust I model showed the relationship of hypertension and B-ALP when the basic covariant was adjusted which is the year. In this adjusted I model, the level of B-ALP decreased by 0.46 unit for hypertensive males, 0.02 unit for hypertensive females, and 0.12 unit for total subjects. After adjusting for the variables of year, anti-cardiovascular disease drugs used, occupation, and the osteoarthritis for adjusted II model, the level of B-ALP increased by 0.28 unit for hypertensive male, 0.09 unit for hypertensive females, and 0.18 unit for total subjects. There was a consistent correlation between hypertension and B-ALP level in males, females, and in total subject. However, all the correlations had no statistical significance.

Table 4
Multivariate Regression for the relationship between hypertension and the B-ALP level(β, 95%CI, P value)

	hypertension	male	female	total
Adjust	No	Reference	Reference	Reference
	Yes	0.46 (-0.23, 1.14) 0.20	0.02 (-0.36, 0.39) 0.93	0.12 (-0.21, 0.45) 0.47
Adjust	No	Reference	Reference	Reference
	Yes	0.28(-0.35, 0.92) 0.39	0.09 (-0.31, 0.50) 0.65	0.18 (-0.16, 0.52) 0.30

Adjust I model adjust for: Year. **Adjust II model adjust for** Year, Anti-hypertension disease drugs used, Occupation, Osteoarthritis

Multivariate Regression for the relationship between hypertension and TRACP.5B level

Table 5 showed the results of multivariate analysis for the relationship between hypertension and TRACP.5B Log2 transform. Adjust I model shows the relationship of hypertension and TRACP.5B when the basic covariant was adjusted which is the year. In this adjusted I model, the levels of TRACP.5B increased by 0.33 unit for hypertensive males, the levels of TRACP.5B decreased by 0.12 Unit for female hypertensive group and 0.01 Unit for total subjects. After adjusting for the variables of Year, Anti-cardiovascular disease drugs used, Occupation, Osteoarthritis, type 2 diabetes, Cardiovascular disease, Cerebral infarction and BMI for adjusted II model, the level of TRACP.5B increased by 0.51 Unit for hypertensive males and 0.03 Unit for the total subjects. The level of TRACP.5B decreased by 0.13 Unit for hypertensive female. All the correlations have no statistical significance.

Table 5
Multivariate Regression for the relationship between hypertension and the TRACP.5B level(β, 95%CI, P value)

	hypertension	**male**	**female**	**total**
Adjust	No	Reference	Reference	Reference
	Yes	0.33(-0.46, 1.11) 0.42	-0.12 (-0.48, 0.23) 0.50	-0.01(-0.34, 0.32) 0.96
Adjust	No	Reference	Reference	Reference
	Yes	0.51(-0.42, 1.44) 0.29	-0.13(-0.54, 0.27) 0.53	0.03(-0.33, 0.39) 0.87
Adjust I model adjust for: Year. **Adjust II model adjust for** Year, Anti-hypertension drugs used, Occupation, Osteoarthritis, type 2 diabetes, Coronary heart disease, Cerebral infarction, BMI				

Multivariate Regression for the relationship between hypertension and 25-OHD level

Table 6 showed the results of multivariate analysis for the relationship between hypertension and 25-OHD Log2 transform. Adjust I model showed the relationship of hypertension and 25-OHD when the basic covariant was adjusted which is the year. In this adjusted I model, the level of CT decreased by 0.31 unit for hypertensive males (95% CI: -0.54 to -0.09, P = 0.01), and 0.02 unit for hypertensive males (95% CI: -0.16 to -0.13, P = 0.84). After adjusting for the variables of year, anti-cardiovascular disease drugs used, occupation, type 2 diabetes, and cardiovascular disease for adjusted II model, there was also a consistent correlation between hypertension and 25-OHD in males (β= -0.34, 95% CI: -0.58 to 0.10, P = 0.01) and in total subjects(β= -0.08, 95% CI: -0.21 to 0.05, P = 0.23). While the level of CT increased by 0.03 unit for hypertensive females in adjusted II model (95% CI: -0.13 to 0.19, P = 0.72).

Table 6
Multivariate Regression for the relationship between hypertension and the 25-OHD level(β, 95%CI, P value)

	hypertension	male	female	total
Adjust	No	Reference	Reference	Reference
	Yes	-0.31 (-0.54, -0.09) 0.01	-0.02(-0.16, 0.13) 0.84	-0.01 (-0.22, 0.02) 0.11
Adjust	No	Reference	Reference	Reference
	Yes	-0.34(-0.58, -0.10) 0.01	0.03(-0.13, 0.19) 0.72	-0.08 (-0.21, 0.05) 0.23

Adjust I model adjust for: Year. **Adjust II model adjust for** Year, Anti-hypertension drugs used, Occupation, type 2 diabetes, Coronary heart disease

Discussion

The relationship between high blood pressure and osteoporosis has been well demonstrated. PTH and angiotensin II receptors have been found on osteoblast cell lines that directly regulate bone turnover[6, 7]. Hypertensive patients have decreased intestinal calcium absorption, increased urinary calcium excretion, and decreased plasma vitamin D concentrations which result in changes in PTH expression and secretion which is critical for bone anabolic and catabolic effects[5–7]. In this study, after the potential confounders were adjusted, 25-OHD level was significantly lower in hypertensive male group than that in male without hypertension group. The reduction of 25-OHD level might lead to the imbalance of calcium metabolism, bone metabolism and mineralization through the promotion of the synthesis and secretion of PTH. However, there were no serum PTH data, so the role of PTH in osteoporotic patients with hypertension cannot be estimated.

Serum biochemical indicators are commonly used to evaluate bone metabolism. Detection of serum bone turnover markers plays an important role in the typing, prevention and treatment of osteoporosis. OC is an active polypeptide secreted and synthesized by osteoblasts, which reflect the function and activity of osteoblasts. Although, no significant difference was found in relationship between B-ALP and hypertension, the level of OC in postmenopausal women with osteoporosis and hypertension was lower than in osteoporotic patients without hypertension in our results which indicates that hypertension can lead to lower bone formation. However, the relationship between serum OC and hypertension is currently still under debate. Bezerra et al. had studied the differences of serum OC levels in patients with metabolic syndrome. In their study, the hypertensive group had lower level of OC than the non-hypertensive group[11]. In a cross-sectional study that was conducted among 162 subjects, the authors show that the concentration of OC was significantly lower with hypertension than those without hypertension[12]. In addition, there was an observational study of 2241 Chinese people in which the hypertensive male group had a lower serum OC level compared with those in the non-hypertensive group while no difference was found between the two groups of women[13]. In order to further elucidate the role of hypertension in

osteoporosis, more high-quality studies are needed to explore the relationship between blood pressure and serum OC level.

PTH and catecholamines (including adrenaline and angiotensin II) were shown to induce osteoclastogenesis and bone loss through acting on osteoblast precursor cells directly. The result of the case study showed that TRACP.5B level was positively associated with hypertension in univariate or multivariate analysis, but there was no significant difference. TRACP.5B is mainly derived from osteoclasts, which has a strong correlation with the activity of total TRACP. Patients who have metabolic syndrome including type 2 diabetes and Paget disease were shown to have higher serum TRACP.5B level which reflects higher bone resorption. Also, hypertension was found to have no impact on bone resorption, but it requires further investigation.

The case study had several limitations. First, the case study was a retrospective cross-sectional study, so some patients' basic information were not well recorded in detail. Second, the study investigated a relatively small number of patients in a hospital. In the future, large-scale samples and better-quality studies are needed to validate and explain the case findings.

Conclusions

The results from this study demonstrate that, overall, hypertension is related to the level of bone metabolic markers in osteoporosis patients, but the effect of hypertension on bone resorption has not been found. Specifically, the relationship was that hypertension was associated with low OC level in female and low 25-OHD level in male, which may play a role in bone loss.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Affiliated Hospital of Guangdong Medical University (Approval NO. PJ2012026) approved the study.Since our study only obtained the patient's existing examination data, we did not obtain the sensitive information such as the patient's name, let alone the treatment related to hospitalization. So there is no written informed consent. However, it was approved by the ethics committee of the affiliated hospital of guangdong medical university.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

Zhuoqing Hu and Kevin Yang made substantial contributions to the conception and design, analyzed and interpreted the data, performed the literature search, and was the major contributor in the writing of the manuscript. Hao Wei, Zheng Tang, Zhihui Hu and Baitong Chen made substantial contributions to the conception and design and revised the draft critically for important intellectual content. Chengbiao Su and Jinrong Xu made substantial contributions to the conception and design, analyzed and interpreted the data, and revised the draft critically for important intellectual content. All authors read and approved the final manuscript.

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