

# Analysis of the prevalence, risk factors, and clinical characteristics of osteoporosis in patients with essential hypertension

**Hai-Long Wu**

Changchun University of Chinese Medicine

**Jie Yang**

Changchun University of Chinese Medicine

**Yu-Chi Wei**

Changchun University of Chinese Medicine

**Jian-Yu Wang**

Changchun University of Chinese Medicine

**Yu-Yan Jia**

Changchun University of Chinese Medicine

**Luan Li**

Changchun Medical College

**Lu Zhang**

Changchun University of Chinese Medicine

**Yan Lu**

Changchun University of Chinese Medicine

**Xiang-Yang Leng** (✉ [lengxiangy@163.com](mailto:lengxiangy@163.com))

Changchun University of Chinese Medicine

**Zong-Jian Luo**

The Affiliated Hospital to Changchun University of Chinese Medicine

---

## Research Article

**Keywords:** antihypertensive medication, creatinine, essential hypertension, influencing factors, osteoporosis

**Posted Date:** March 10th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1412138/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

# Abstract

## Objectives

The present study investigated the prevalence of osteoporosis (OP) in patients with essential hypertension (EH) in the Changchun community and analyzed the correlation between EH and OP.

## Methods

The study was conducted in 425 patients with EH and 425 healthy controls. Bone mineral density (BMD) and serum creatinine (CR) levels were measured, and the patients' current status was surveyed to analyze the correlation between EH and OP.

## Results

The EH group exhibited lower BMD and higher prevalence of OP than the healthy controls, and this difference was statistically significant ( $\chi^2 = 12.968$ ;  $p = 0.002$ ). However, the difference in OP prevalence was statistically nonsignificant between male and female patients ( $\chi^2 = 1.998$ ;  $df = 1$ ;  $p = 0.157$ ). The risk of developing OP was not significantly different between middle-aged and elderly men and women ( $\chi^2 = 0.228$ ;  $p = 0.633$ ). However, the OP risk in patients with EH varied significantly with different age, body weight, fracture history, nocturnal urination frequency, depression and anxiety status, duration of hypertension, and antihypertensive medication ( $p < 0.05$ ). The two-way analysis of variance suggested an effect of the interaction between different EH prevalence conditions and bone mass conditions on the serum CR values ( $F = 3.584$ ,  $p = 0.028$ , bias  $\eta^2 = 0.008$ ).

## Conclusions

The incidences of OP and low BMD were significantly higher in patients with EH than in healthy controls. Additionally, age, weight, fracture history, nocturnal urination frequency, depression and anxiety, duration of hypertension, and antihypertensive medication were the risk factors for OP in patients with EH. Moreover, serum CR levels in patients with different bone mass profiles were strongly influenced by the presence or absence of EH, and the expression of serum CR levels differed significantly with the interaction of this factor.

## Introduction

Osteoporosis (OP) and essential hypertension (EH) occur commonly and often as coexisting diseases in both the middle-aged and elderly populations [1]. With increasing age and life expectancy, the prevalence of OP and EH, either alone or in combination, increases considerably [2]. According to a 2019 study [3], the incidence of reduced bone mineral density (BMD) is significantly higher in patients with EH than in healthy individuals. Additionally, hypertension treatment affects BMD and exacerbates OP [4]. In the long term, EH patients will be more likely to develop OP [5]. EH and OP exhibit several common risk factors [6]. Because of a significant correlation between EH and BMD, the risk factors associated with EH serve as both risk and protective factors for OP. Although the underlying mechanisms remain unclear, these two diseases may share the same etiology

[7]. OP has a correlation with the pathogenesis of hypertension [8]. traditionally, the decline in gonadal hormones has been studied as the sole hormonal determinant for the loss of bone mineral density in osteoporosis. However, recent studies have identified receptors for numerous non-gonadal hormones such as angiotensin II which is also involved in the pathogenesis of metabolic syndrome risk factors, particularly hypertension and obesity.

This article conducts clinical epidemiological investigation based on this connection, and obtains the relevant risk factors between EH and OP through statistical methods. In clinical diagnosis and treatment, blood pressure control is necessary for EH patients, and blood pressure control drugs contain some components that affect bone quality, such as the interaction of calcium ions and dipine [9]. Whether the risk factors of EH patients, such as the application of different types of antihypertensive drugs, will aggravate/reduce the occurrence of OP. Based on the above findings, we consider whether it is possible to avoid antihypertensive drugs that have an impact on bone quality when administering drugs to people with OP risk factors in EH clinical diagnosis and treatment.

## Methods

### Subject selection criteria

The present study was conducted in 425 patients, aged between 50 and 80 years, diagnosed with EH and having at least 2 years of disease period, consistent with the chronic disease. The control group comprised an equal number of healthy individuals in the same age group. We use questionnaires to assign hypertensive patients, because patients are a known factor in whether they have hypertension. In addition, we screened patients with a history of hypertension for more than 2 years, and judged their hypertension and their medication status through question and answer, and provided basic data support for subsequent analysis of related risk factors. The selection method of the control group is to first select the samples that meet the results by gender and age matching in the overall sample, and then select the samples that meet the matching results according to the ratio of 1:1 by the random number table method.

Patients with the following conditions were excluded from the study: pituitary, thyroid, parathyroid, adrenal, or gonadal diseases or tumors, severe heart, liver, kidney, central nervous system or psychiatric diseases, type 1 or type 2 diabetes and chronic metabolic disorders other than OP, dependence on drugs other than antihypertensive medication during the study period, Spinal idiopathic disease, Receive anti-osteoporosis treatment and other major medical conditions such as infection or cancer. Pregnant or lactating women were also excluded from the study.

The general information, sociodemographic data, and medical status of all the participants were collected through questionnaire. Detailed medical history of the participants was recorded, physical examination and laboratory tests were conducted to exclude subjects with abnormal or certain medical conditions. Study procedures were explained in detail and signed informed consent forms were obtained from all the participants. all methods were carried out in accordance with relevant guidelines and regulations. The Institutional Review Board of Changchun University of Traditional Chinese Medicine Hospital approved the study.

### Representational Considerations

Luyuan District and Chaoyang District of Changchun City are old urban areas that cover a wide range of risk exposures. In the study cohort, there were patterns of disease that may require further research to ensure accuracy and completeness in self-reporting, as well as to ensure accuracy in researchers' abilities to collect the necessary data.

BMI is calculated based on weight and height, and related studies have shown that [10-12] simple obesity and overweight are protective factors for osteoporosis and risk factors for EH. Therefore, in this study, weight was selected as one of the independent indicators.

eGRF is one of the classic indicators used to evaluate renal function, and the reason for including serum creatinine in this study is as follows: 1. Serum creatinine has a positive correlation with the patient's hypertension state [13], 2. Serum creatinine has a negative correlation with OP patients [14]. Therefore, we included the level of serum creatinine in the study to obtain the link between EH and OP.

The people who are susceptible to menopausal syndrome are women. The reason why women are in this state is caused by abnormal hormone levels during menopause and other factors. The scope is wide and it is difficult to extract actual data. but in physiological state, There will be a series of physiological and psychological changes, so we include anxiety and depression as an indicator to evaluate menopausal status.

The level of vitamin D is easily affected by the season, and the test value taken at one time may not reflect the overall change of the patient's own vitamin D, which is also one of the shortcomings in this study, At the same time, patients with a history of hypertension have a more regular way of taking medications, and they often have taken antihypertensive drugs at the time of the test. Therefore, the test at this time is a post-medication test and cannot reflect their original blood pressure status. If a patient with hypertension does not take the medicine, a series of tests are not appropriate for the patient and violates the ethical standards.

In addition, this study did not include the "smoking status", because for patients with chronic hypertension, clinically, while providing drug treatment, they will also give medical advice to quit smoking and drinking. This will lead to patients with chronic hypertension and smoking will actively choose to quit smoking in order to control related cardiovascular diseases. Including smoking status as a reference index compared with the control group will produce bias. Therefore, the "smoking status" was not included as a reference in this study.

### **BMD assay and demographic characteristics in patients and controls**

BMD levels in the lumbar spine and left hip were determined using dual energy X-ray densitometry (DXA), Discovery Wi (S/N 88317), produced by the American Hologic manufacturer. According to The WHO website provides the relationship between the measurement of BMD value (T value) and osteoporosis <http://slideplayer.com/slide/4493823/>. the patients were classified into the following groups: normal bone mass (T value  $\geq -1.0$ ), osteopenia ( $-2.5 < \text{T value} < -1.0$ ), and osteoporosis (T value  $\leq -2.5$ )<sup>[15]</sup>. Anthropometric variables, weight (kg) and height (cm), were measured in a standardized manner.

In this study, specific professionals are arranged to perform BMD testing. Users must conduct strict quality control before testing patients every day. After completing the diagnostic tests for some functional indicators and scanning the lumbar vertebral phantom provided by the manufacturer, check the diagnostic report. If it fails the first time, it should be done a second time. If there are two consecutive failures or the difference between the

two consecutive scans and the baseline value is greater than 1.5%, the researcher must contact the manufacturer for maintenance to find out the cause. In addition, if the inspector finds a deviation from the baseline trend when looking at the quality control chart, he should check whether it is a calibration drift. For the subjects, the height and weight must be measured before the bone density measurement, in addition, the true date of birth (year/month/day) must be provided in order to obtain more accurate measurement results. The accessories worn by watches, bracelets, and rings should also be removed when measuring.

### **Data processing and statistical analysis**

EpiData 2.1b was used to establish the database, and SPSS software (version 26.0) in Windows 10 was used for statistical processing, with a two-sided p value of 0.05. The observations in the present study were independent of each other. No significant outlier was present in the observed variables, which were nearly normally distributed within each group and exhibited equal variance. The following tests were selected according to the type of variable and the need for clinical analysis:

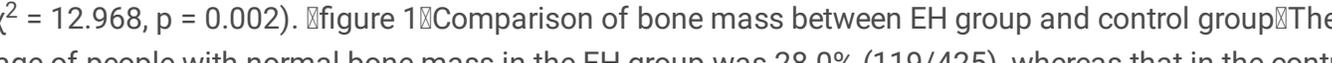
1. Independent sample t-test was used to analyze group differences in age and body weight between the EH group and the control group.
2. The Mann–Whitney U test was used to analyze differences in the BMD T-score and CR levels between the EH group and the control group.
3. For the count data, the Pearson and chi-square tests were used if the expected frequency of all cells was  $>5$ , whereas Fisher's exact test was used if the expected frequency was  $<5$ . Analysis of covariance was used to control for the effects of confounding variables, and Bonferroni correction was applied to adjust for multiple tests.
4. The chi-square test was used to analyze differences between the EH group and the control group in terms of gender and bone mass. The clinical correlations of gender, age, fracture history, nocturnal urination frequency, depression and anxiety status, duration of EH, and antihypertensive drugs with bone mass status were also analyzed within the EH group. Additionally, the column proportions were compared and p values were adjusted (through Bonferroni method) in the Z-test to compare between-group differences in demographic and clinical variables for different bone mass profiles and intragroup differences (within the EH group) in the nocturnal urination frequencies, depression and anxiety status, duration of EH, and antihypertensive medication in a two-by-two comparison.
5. The Mantel–Haenszel chi-square test was used to determine whether a linear correlation exist between age and OP incidence within the EH group, and the strength of the association was determined according to the Pearson's correlation coefficient, R.
6. Two-factor analysis of variance (ANOVA) was used to evaluate the effect of different EH prevalence and bone mass conditions on CR. Box plots were used to test for outliers, the Shapiro–Wilk test was used to determine data normality, and Levene chi-square test was used to determine isotropy.

## **Results**

### **Demographic characteristics of patients and controls**

The effects of confounding factors such as sex and age were excluded from the present study. Table 1 summarized the mean age of patients was  $64.6 \pm 6.7$  years, whereas that of the controls was  $64.0 \pm 7.0$  years. The two groups exhibited no significant difference in terms of age and sex ( $p > 0.05$ ).

### **OP prevalence in patients and controls**

Table 1 showed a significant difference was observed in the bone mass between the EH group and the control group ( $\chi^2 = 12.968$ ,  $p = 0.002$ ). The percentage of people with normal bone mass in the EH group was 28.0% (119/425), whereas that in the control group was 39.3% (167/425). The incidence of OP was 30.4% (129/425) in the EH group and 23.3% (99/425) in the control group. This difference was statistically significant ( $\chi^2 = 12.968$ ,  $p = 0.002$ ) even after controlling for sociodemographic confounding factors by using logistic regression. Additionally, the incidence of low BMD (osteopenia + osteoporosis) was 72.0% (306/425) in the EH group and 60.7% (258/425) in the control group, and this difference also remained statistically significant after adjusting for sociodemographic confounding variables ( $p < 0.01$ ). BMD levels observed in the EH group were significantly lower than those in the control group ( $U = 83167.000$ ,  $p = 0.046$ ). Additionally, no significant sex predilection was observed in the prevalence of OP in the two groups ( $\chi^2 = 1.998$ ,  $df = 1$ ,  $p = 0.157$ ), however, female patients in the EH group exhibited a significantly higher prevalence of low BMD (osteoporosis + osteopenia) (male patients: 57.1%, female patients: 71.6%,  $\chi^2 = 7.855$ ,  $df = 1$ ,  $p = 0.005$ ), although this difference was not observed in the control group ( $\chi^2 = 0.455$ ,  $df = 1$ ,  $p = 0.500$ ). Additionally, a significant sex predilection was observed in the BMD T-score among the patients (male patients:  $-1.19 \pm 1.55$ , female patients:  $-1.70 \pm 1.34$ ,  $F = 6.142$ ,  $df = 423$ ,  $p = 0.001$ ), which persisted even after controlling for confounding factors ( $p < 0.01$ ). Further analysis exhibited that although the body weight of patients with EH was significantly higher than that of healthy controls (EH patients:  $66.15 \pm 10.11$ , healthy controls:  $62.23 \pm 9.21$ ,  $t = 5.760$ ,  $p < 0.001$ ), the CR levels between the two groups did not vary significantly (EH group:  $70.68 \pm 0.88$ , healthy controls:  $69.69 \pm 0.72$ ,  $p = 0.934$ ).

Bone densitometry examination of BMD in the lumbar spine and hip indicated that the prevalence of OP and low BMD in the EH group was significantly higher than that in the control group. Additionally, BMD levels were significantly lower in patients with EH than in healthy controls. No sex predilection was observed in the prevalence of OP in both the EH and control groups. However, the prevalence rate of low BMD in the EH group was significantly higher in female patients than in male patients, whereas no such difference was observed in the control group. Additionally, female patients exhibited significantly lower BMD T-scores than male patients.

### **Demographic and clinical variables in the non-OP and OP populations of the EH group**

**According to Table 2**, a comparison of the OP and non-OP populations in the EH group indicated the prevalence of OP in 32 of 112 men (28.6%) and 97 of 313 women (31.0%). Additionally, the analysis of cross-tabulation results exhibited that the OP risk was similar between middle-aged and elderly male and female patients, with no statistically significant difference (Pearson  $\chi^2 = 0.228$ ,  $p = 0.633$ ). However, a linear correlation was observed between age and OP incidence ( $\chi^2 = 8.991$ ,  $p = 0.001$ ). Pearson correlation results ( $R = 0.146$  and  $p = 0.003$ ) indicated that the OP incidence increased with age. The body weight of the non-OP population ( $65.86 \pm 9.84$  Kg) was similar to that of the OP population ( $66.80 \pm 10.71$  Kg), with no statistically significant difference ( $t = 0.874$ ,  $p = 0.383$ ). A total of 92 of the 329 participants (28.0%) with no fracture history and 37 of the 96 (38.5%)

patients with previous fracture exhibited OP. This result in combination with the cross-tabulation results indicated that the OP risk was higher in the population with previous fractures ( $\chi^2 = 3.934$ ,  $p = 0.047$ ). With regards to the results of the investigation on OP risk with nighttime urination frequency, OP incidence was noted in 20 of the 102 (19.6%) individuals who never got up at night for urination, 79 of the 238 (33.2%) individuals who urinated 1–2 times at night, and 30 of the 85 (35.3%) individuals who urinated >3 times at night, with statistically significant differences among the three groups ( $\chi^2 = 7.461$ ,  $p = 0.024$ ). A two-by-two comparison revealed a statistically significant difference in the OP risk between those who never got up at night and those who urinated 1–2 times and >3 times at night ( $p < 0.05$ ), whereas no significant difference was observed in the OP risk between those who urinated 1–2 times at night and those who urinated >3 times at night ( $p > 0.05$ ). The survey on depression and anxiety in EH patients revealed that OP occurred in 84 of the 315 patients (26.7%) who were not depressed and anxious, 38 of the 95 patients (40.0%) who exhibited mild depression and anxiety, and 9 of the 14 patients (64.3%) who exhibited moderate depression and anxiety. Fisher's exact test exhibited that the OP risk was not equal among the study subjects with different depressive and anxiety states, indicating that the OP risk was statistically different in at least two groups ( $p = 0.001$ ). A two-by-two comparison revealed a statistically significant difference in the OP risk between those who never got up at night and those who urinated 1–2 times and >3 times at night ( $\chi^2 = 6.208$ ,  $p = 0.013$ ). However, no difference was observed in the OP risk between those who urinated 1–2 times at night and those who urinated >3 times at night ( $p > 0.05$ ). Based on the duration of persistence of EH, the patients were divided into four groups: 2–5 years, 6–10 years, 11–19 years, and more than 20 years. The incidence of OP was noted in 32 of the 158 patients (20.3%) with 2–5 years of disease, 49 of the 137 patients (35.8%) with 6–10 years of disease, 21 of the 52 patients (40.4%) with 11–19 years of disease, and 27 of the 78 patients (34.6%) with more than 20 years of disease. The difference between the four groups was statistically significant ( $\chi^2 = 12.669$ ,  $p = 0.005$ ). A two-by-two comparison revealed a statistically significant difference in the OP risk between those with 2–5 years of disease and those with 6–10 years of disease ( $p < 0.05$ ). However, no difference in the OP risk was observed among patients with more than 5 years of disease.

The OP risks were similar in middle-aged and elderly men and women, with no significant differences. However, age and OP exhibited a linear correlation, and the incidence of OP increased with age. Additionally, the body weight of the non-OP population was approximately similar to that of the OP population. However, the OP risk was higher in those with previous fractures. Other risk factors for OP identified were: age, fracture history, nocturnal urination frequency, depression and anxiety status, duration of hypertension, and antihypertensive medication.

### **OP in patients treated with different antihypertensive medications**

In the EH group, the proportion of patients who received only one antihypertensive medication was 89.2% (264/296) in the non-OP population, whereas that in the OP population was 10.8% (32/296). The proportion receiving a combination of two or three antihypertensive medications was 81.4% (105/129) in the non-OP population and 18.6% (24/129) in the OP population. The present study demonstrated a statistically significant difference in the OP risk between patients on a combination of antihypertensive medications and those on a single antihypertensive medication ( $\chi^2 = 4.770$ ,  $df = 1$ ,  $p = 0.029$ ). Furthermore, the EH patients were divided into seven groups based on the type of antihypertensive medication used. **According to Table 3**, OP occurred in 17 of 30 (56.7%) individuals who were not on regular medication, 77 of 202 (38.1%) individuals who were on oral

amlodipine, and 8 of 20 (40.0%) individuals who were on oral nifedipine, 5 of 32 (15.6%) individuals who took oral propranolol, 5 of 31 (36.1%) individuals who took oral captopril, 9 of 80 (11.3%) individuals who took oral valsartan, and 8 of 30 individuals who took proprietary Chinese medicines (pCMs) (specific ingredients unknown). The difference in OP incidence between the seven groups was statistically significant ( $\chi^2 = 36.722$ ,  $p < 0.000$ ). A two-by-two comparison revealed statistically significant differences in the OP risk in patients who did not take the drug regularly and those who took oral propranolol, captopril, valsartan, and oral pCMs ( $p < 0.05$ ). However, no significant differences were observed in the OP risk in patients who did not take the drug regularly and those who took oral amlodipine or nifedipine. The difference in the OP risk between patients on oral amlodipine or nifedipine and those on oral propranolol, captopril, and valsartan was statistically significant ( $p < 0.05$ ).  
figure 2: Two-by-two comparison based on the  $\chi^2$  test for different antihypertensive medication applications.

This study showed that the combined treatment of antihypertensive drugs increased the incidence of OP compared with EH subjects who only used one type of antihypertensive drug alone. In the comparison of different types of antihypertensive drugs taken by EH patients, it is found that the risk of OP in patients taking propranolol, captopril, and valsartan is relatively lower than other types of antihypertensive drugs.

### **Effect of differences in EH and OP prevalence on CR**

The Mann–Whitney U test was used to determine whether a difference in CR levels existed between the non-OP and OP populations in the EH group (Table 2). The histogram exhibited an inconsistent shape of the distribution of CR levels in the two groups. The mean rank order of CR levels in the non-OP group was 225.17, whereas that in the OP group was 185.07. The Mann–Whitney U test exhibited a statistically significant difference in CR levels between the two groups ( $U = 15489.000$ ,  $p = 0.002$ ). Further, the two-factor ANOVA exhibited that the data in this study had no outliers, the residuals were close to normal distribution ( $p > 0.05$ ), and all variables exhibited equal variance ( $p > 0.05$ ). In terms of CR value, an interaction was observed between EH prevalence conditions and bone mass conditions ( $F = 3.584$ ,  $p = 0.028$ , bias  $\eta^2 = 0.008$ ). The separate effects analysis suggested that the effect on CR values differed among the study subjects with different bone mass conditions and different EH prevalence conditions: the EH study subjects ( $F = 6.346$ ,  $p = 0.002$ , bias  $\eta^2 = 0.015$ ), and between study subjects with different EH prevalence conditions in different bone mass conditions: the population with normal bone mass ( $F = 10.997$ ,  $p = 0.001$ , bias  $\eta^2 = 0.013$ ).

No significant difference was observed in the CR levels between the EH and control groups, and CR concentrations were significantly higher in the non-OP population than in the OP population within the EH group. An interaction between different EH prevalence and different bone mass conditions had an influence on CR values. Moreover, serum CR levels in the study subjects with different bone mass conditions were more affected by the presence or absence of EH. The expression of CR levels varies significantly under the interaction of EH, and the application of CR in patients with EH may seriously reduce the diagnostic efficacy of OP.

## **Discussion**

EH and OP are two major age-related diseases [16] that contribute to considerable morbidity and mortality in the middle-aged and elderly population by inducing cardiovascular disease, fragility fractures, and associated complications and sequelae [17]. Both EH and OP are multifactorial diseases, in which factors such as genetics and lifestyle contribute to the pathogenesis. The EH and OP incidences increase with increasing life expectancy. Studies have exhibited that EH and OP share common risk factors and similar pathological mechanisms [18]. N. Hijazi et al [19] believe that there is no connection between EH and OP, while H. Poudyal, et al [20] studies have shown that they are connected. Based on the above contradictory viewpoints, we considered it like this: HTN was defined as blood pressure  $\geq 130/85$  mmHg or a history of hypertension medication. However, the article does not specify the length of the disease for hypertension. Our study included people with hypertension for more than two years. From a clinical point of view, this group of patients has been taking regular medication to control blood pressure. And because the change of BMD in patients with osteoporosis is a long-term process, we set the history of hypertension to 2 years. This time period is enough for us to discover the correlation between EH and BMD changes, and it can be analyzed as a related risk factor. In this research, it has indeed confirmed that there is a certain connection between the two. The present study exhibited a significantly higher OP prevalence in the EH group than in the control group, suggesting that EH may increase OP risk. This finding is consistent with that of other studies [18]. The present study also identified several OP risk factors such as gender, age, history of fracture, CR, nocturnal urination frequency, depressive and anxiety status, duration of hypertension, and application of antihypertensive medications in patients with EH, suggesting that the concurrence of EH and OP may accelerate disease progression, thereby creating a vicious cycle.

The mechanism underlying the occurrence of OP in patients with hypertension is not fully understood. However, the renin-angiotensin–aldosterone system (RAAS) is known to play a crucial role in blood pressure regulation and fluid homeostasis [6]. The role of RAAS in OP has also been reported in experimental studies, where osteoblasts exhibited components of RAAS, including angiotensin 1 receptor (AT1R), angiotensin 2 receptor (AT2R), and aldosterone receptor. In an experimental study [15], RAAS activation or chronic angiotensin II (AngII) injection increased bone resorption, whereas lack of AT1R was associated with an increase in bone strength. AngII can also induce mitochondrial oxidative stress and damage to mesenchymal-derived osteoblasts by reducing sirtuin (SIRT) 1 expression. In experimental models [16], SIRT1 expression has been found to be positively associated with bone mass. In patients with EH, the use of RAAS inhibitors including ACE inhibitors (for 2 years or less) was associated with a considerable risk of fracture; however, their long-term use was associated with a reduced fracture risk [9, 15, 17], which is consistent with the results of the current study. Additionally, the present study exhibited that the use of calcium channel blocking drugs increased the OP risk in patients with EH, which may be related to the inhibition of extracellular  $\text{Ca}^{2+}$  inward flow by this class of drug. Because antihypertensive medications are being widely used in elderly patients, and EH and OP often coexist, the effect of antihypertensive therapy on bone and fracture risk should be considered prior to its clinical application.

The present study focused on body weight and CR levels. On one hand, body weight and CR levels display a complex trend under the influence of both diseases. The health risk of obesity on EH may exceed its protective impact on skeletal health in the middle-aged and elderly populations [18]. Although weight gain may reduce the OP risk to some extent, the reduction is quite limited and may significantly increase the risk of EH. On the other hand, weight loss may be associated with a reduced risk of hypertension and no considerable increase in OP risk. A related study [21] exhibited that the addition of renal function measurements as a risk factor for fracture

did not improve the OP risk factors (e.g., age, weight, and hip BMD) in postmenopausal women without moderate or severe coronary artery disease. Additionally, the present study provided circumstantial evidence that although increasing CR measurements may improve the fracture risk prediction to some extent, the application of CR in EH patients may seriously reduce the diagnostic efficacy of OP in generally asymptomatic middle-aged and elderly adults.

### **limitation**

The current study considered few vital confounding factors, such as sex and personal history of fracture, and excluded patients who had EH for the preceding 2 years, which allowed us to obtain a more accurate and reliable estimate of the correlation. However, the present study has certain limitations. First, the study population was heterogeneous in terms of comorbidity and disease severity. Second, the effect of a particular antihypertensive medication on bone may depend on the duration of its use, making it impossible to determine the EH severity. Third, failure to use propensity scoring methods to better eliminate confounding. Additionally, obtaining a causal relationship between influencing factors and OP incidence was difficult. Finally, information related to cardiovascular disease was obtained from medical records rather than objective examinations. Although we tried our best to obtain objective data, some bias still existed in the individual lifestyle data. Therefore, based on the present study, prospective cohort studies should be considered for further research in this domain.

## **Conclusion**

Incidences of both EH and OP have become common in the elderly population, and EH may be a strong causative factor for OP. The extent to which the common risk factors for these diseases affect the bone mass status warrants further definitive quantitative analysis in the future. Therefore, we recommend that along with efficient screening for hypertension, bone density testing should be promoted in the elderly population, especially in patients diagnosed as having hypertension, for early screening and early intervention. Considering the closely related manifestations of these two diseases, proper blood pressure control and rational use of medications in the middle-aged and elderly populations may improve bone health and prevent the occurrence of fragility fractures in patients with hypertension.

## **Declarations**

### **Conflict of Interest**

Hai-Long Wu , Jie Yang , Yu-Chi Wei , Jian-Yu Wang , Yu-Yan Jia , Luan Li , Lu Zhang , Yan Lu , Xiang-Yang Leng , Zong-Jian Luo , The authors declare no conflict of interests.

### **Author Contributions**

H-LW, Z-JL, LL, and X-YL contributed to the conception and design of the research. JY, Y-CW, J-YW, and Y-YJ performed the experiments and analyzed the data. H-LW, Z-JL, and LZ interpreted the results. YL and JY prepared the figures. H-LW drafted the manuscript, and LL, Y-CW and J-YW edited and revised the manuscript. All authors approved the final version of the manuscript.

## Funding

This work was supported by grants from the National Clinical research base of TCM project (grant number JDZX2015077), Jilin Province Department of Education research project (grant number JJKH20210948KJ), Natural Science Foundation of Jilin Province (grant number 20210101233JC). The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the article for publication.

## Data Availability Statement

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

## Patient consent statement

Study procedures were explained in detail and Written informed consent was obtained from either the individual or guardian participant.

## Ethics approval statement

The experimental protocol was developed in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the Human Ethics Committee of The Affiliated Hospital to Changchun University of Chinese Medicine (CCZYFYLL2017-029, CCZYFYLL2021-043). Written informed consent was obtained from either the individual or guardian participant.

## Consent for publication

Not Applicable

## Acknowledgements

We would like to thank Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine for their assistance in this study.

## References

1. Wright N, Saag K, Dawson-Hughes B, Khosla S, Siris EJOiajearocbtEFfO, USA tNOFot: **The impact of the new National Bone Health Alliance (NBHA) diagnostic criteria on the prevalence of osteoporosis in the United States: supplementary presentation.** 2017, **28**(11):3283–3284.
2. Fujita TJOiajearocbtEFfO, USA tNOFot: **Osteoporosis: past, present and future.** 1997:S6-9.
3. Gutzwiller J, Richerich J, Stanga Z, Nydegger U, Risch L, Risch MJBg: **Osteoporosis, diabetes, and hypertension are major risk factors for mortality in older adults: an intermediate report on a prospective survey of 1467 community-dwelling elderly healthy pensioners in Switzerland.** 2018, **18**(1):115.
4. Chai H, Ge J, Li L, Li J, Ye YJBmd: **Hypertension is associated with osteoporosis: a case-control study in Chinese postmenopausal women.** 2021, **22**(1):253.

5. MacGregor GA, Cappuccio FP: **The kidney and essential hypertension: a link to osteoporosis?** *Journal of hypertension* 1993, **11**(8):781–785.
6. Asaba Y, Ito M, Fumoto T, Watanabe K, Fukuhara R, Takeshita S, Nimura Y, Ishida J, Fukamizu A, Ikeda K *et al*: **Activation of renin-angiotensin system induces osteoporosis independently of hypertension.** 2009, **24**(2):241–250.
7. Shu X, Mei M, Ma L, Wang Z, Yang S, Hu J, Song Y, He W, Luo T, Cheng Q *et al*: **Postmenopausal osteoporosis is associated with elevated aldosterone/renin ratio.** 2018, **32**(7):524–530.
8. Poudyal H, Brown LJC *et al*: **Osteoporosis and its association with non-gonadal hormones involved in hypertension, adiposity and hyperglycaemia.** 2013, **14**(14):1694–1706.
9. Sasaki H, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohhira M, Oyama T, Miyashita Y *et al*: **Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy.** 2009, **16**(5):568–575.
10. Fassio A, Idolazzi L, Rossini M, Gatti D, Adami G, Giollo A, Viapiana OJE, EWD wd: **The obesity paradox and osteoporosis.** 2018, **23**(3):293–302.
11. Gkastaris K, Goulis DG, Potoupnis M, Anastasilakis AD, Kapetanios G: **Obesity, osteoporosis and bone metabolism.** *Journal of musculoskeletal & neuronal interactions* 2020, **20**(3):372–381.
12. Proietto JJF: **Obesity and Bone.** 2020, **9**.
13. Bagheri B, Radmard N, Faghani-Makrani A, Rasouli MJ *et al*: **Serum Creatinine and Occurrence and Severity of Coronary Artery Disease.** 2019, **73**(3):154–156.
14. Park BK, Yun KY, Kim SC, Joo JK, Lee KS, Choi OH: **The Relationship between Renal Function and Bone Marrow Density in Healthy Korean Women.** *Journal of menopausal medicine* 2017, **23**(2):96–101.
15. Carbone L, Vasan S, Prentice R, Harshfield G, Haring B, Cauley J, Johnson KJO *et al*: **The renin-angiotensin aldosterone system and osteoporosis: findings from the Women's Health Initiative.** 2019, **30**(10):2039–2056.
16. Shuai B, Yang Y, Shen L, Zhu R, Xu X, Ma C, Lv L, Zhao J, Rong JJ *et al*: **Local renin-angiotensin system is associated with bone mineral density of glucocorticoid-induced osteoporosis patients.** 2015, **26**(3):1063–1071.
17. Aluoch A, Jessee R, Habal H, Garcia-Rosell M, Shah R, Reed G, Carbone LJ *et al*: **Heart failure as a risk factor for osteoporosis and fractures.** 2012, **10**(4):258–269.
18. Sirola J, Rikkinen T, Tuppurainen M, Honkanen R, Kröger HJM: **Should risk of bone fragility restrict weight control for other health reasons in postmenopausal women?—A ten year prospective study.** 2012, **71**(2):162–168.
19. Hijazi N, Alourfi Z: **Association between Hypertension, Antihypertensive Drugs, and Osteoporosis in Postmenopausal Syrian Women: A Cross-Sectional Study.** *Advances in medicine* 2020, **2020**:7014212.
20. Poudyal H, Brown L: **Osteoporosis and its association with non-gonadal hormones involved in hypertension, adiposity and hyperglycaemia.** *Current drug targets* 2013, **14**(14):1694–1706.
21. McCarthy J, Rule A, Achenbach S, Bergstralh E, Khosla S, Melton LJM *et al*: **Use of renal function measurements for assessing fracture risk in postmenopausal women.** 2008, **83**(11):1231–1239.

## Tables

**Table 1 Demographic characteristics of the EH group and the control group**

	EH group (N = 425)	Control group (N = 425)	Test value	p
<b>Age</b>	64.60 ± 6.70	63.96 ± 7.00	T = 1.358	0.173
<b>Sex</b>			$\chi^2 = 0.000$	1.000
Male	112 (30.59%)	112 (27.65%)		
Female	313 (69.41%)	313 (72.35%)		
<b>Bone mass conditions</b>			$\chi^2=12.968$	0.002
Normal	119 <sub>a</sub> (28.0%)	167 <sub>b</sub> (39.3%)		
Osteopenia	177 <sub>a</sub> (41.6%)	159 <sub>a</sub> (37.4%)		
Osteoporosis	129 <sub>a</sub> (30.4%)	99 <sub>b</sub> (23.3%)		
<b>Lumbar spine T value</b>	-1.54 ± 1.43	-1.34 ± 1.45	U = 83167.000	0.046
<b>Body weight (kg)</b>	66.15 ± 10.11	62.23 ± 9.21	T = 5.760	< 0.001
<b>Creatinine (CR)</b>	70.68 ± 0.88	69.69 ± 0.72	U = 90610.000	0.934

**Table 2 Demographic and clinical characteristics of patients having EH with and without OP**

	Non-OP group (N = 296)	OP group (N = 129)	Test value	P
<b>Sex</b>			$\chi^2 = 0.228$	0.633
Male	80 (27.0%)	32 (24.8%)		
Female	216 (73.0%)	97 (75.2%)		
<b>Age</b>			$\chi^2 = 9.015$	0.011
50–59 yrs	69 <sub>a</sub> (23.3%)	17 <sub>b</sub> (13.2%)		
60–69 yrs	154 <sub>a</sub> (52.0%)	65 <sub>a</sub> (50.4%)		
70–79 yrs	73 <sub>a</sub> (24.7%)	47 <sub>b</sub> (36.4%)		
<b>Body weights</b>	65.86 ± 9.84	66.80 ± 10.71	U = 19583.000	0.673
<b>Fracture history</b>			$\chi^2 = 3.934$	0.047
None	237 (80.1%)	92 (71.3%)		
Yes	59 (19.9%)	37 (28.7%)		
<b>Nocturnal urination frequency</b>			$\chi^2 = 7.461$	0.024
None	82 <sub>a</sub> (27.7%)	20 <sub>b</sub> (15.5%)		
1–2 times	159 <sub>a</sub> (53.7%)	79 <sub>a</sub> (61.2%)		
3 or more	55 <sub>a</sub> (18.6%)	30 <sub>a</sub> (23.3%)		
<b>Depression/anxiety status</b>			$\chi^2 = 8.751$	0.013
None	231 <sub>a</sub> (78.3%)	84 <sub>b</sub> (65.1%)		
Mild	57 <sub>a</sub> (19.3%)	38 <sub>a</sub> (29.5%)		
Moderate	7 <sub>a</sub> (2.4%)	7 <sub>a</sub> (5.4%)		
<b>Course of hypertension</b>			$\chi^2 = 12.669$	0.005
2–5 years	126 <sub>a</sub> (42.6%)	32 <sub>b</sub> (24.8%)		
6–10 years	88 <sub>a</sub> (29.7%)	49 <sub>a</sub> (38.0%)		
11–19 years	31 <sub>a</sub> (10.5%)	21 <sub>a</sub> (16.3%)		
more than 20 years	51 <sub>a</sub> (17.2%)	27 <sub>a</sub> (20.9%)		
<b>Drug combination</b>			$\chi^2 = 4.770$	0.029
Only one	264 (89.2%)	105 (81.4%)		
2 or 3	32 (10.8%)	24 (18.6%)		

<b>Types of antihypertensive medication application</b>			36.722	< 0.000
Irregular use	13 (4.4%)	17 (13.2%)		
Amlodipine	125 (42.2%)	77 (59.7%)		
Nifedipine	12 (4.1%)	8 (6.2%)		
Propranolol	27 (9.1%)	5 (3.9%)		
Captopril	26 (8.8%)	5 (3.9%)		
Valsartan	71 (24.0%)	9 (7.0%)		
Proprietary Chinese Medicine (pCM)	22 (7.4%)	8 (6.2%)		
<b>CR</b>	73.95 ± 18.11	69.35 ± 17.05	U = 15489.000	0.002

**Table 3 Two-by-two comparison based on the  $\chi^2$  test for different antihypertensive medication applications**

	Irregular	Amlodipine	Nifedipine	Propranolol	Captopril	Valsartan	pCMs	Total
<b>Non-OP</b>	13 <sub>a</sub> (43.3%)	125 <sub>a,b</sub> (61.9%)	12 <sub>a,b,c</sub> (60.0%)	27 <sub>d,e</sub> (84.4%)	26 <sub>c,d,e</sub> (83.9%)	71 <sub>e</sub> (88.8%)	22 <sub>b,c,d</sub> (73.3%)	296 (69.6%)
<b>OP</b>	17 <sub>a</sub> (56.7%)	77 <sub>a,b</sub> (38.1%)	8 <sub>a,b,c</sub> (40.0%)	5 <sub>d,e</sub> (15.6%)	5 <sub>c,d,e</sub> (16.1%)	9 <sub>e</sub> (11.3%)	8 <sub>b,c,d</sub> (26.7%)	129 (30.4%)
<b>Total</b>	30 (100%)	202 (100%)	20 (100%)	32 (100%)	31 (100%)	80 (100%)	30 (100%)	425 (100%)

Each subscript letter indicates a subset of different "antihypertensive drug application categories". At the 0.05 level, there is no significant difference between the column ratios of these categories.

## Figures

### Figure 1

See image above for figure legend

### Figure 2

See image above for figure legend