Cardiovascular disease is a risk factor for osteoporosis: a case-control study in Chinese women

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Abstract

Background: Osteoporosis and cardiovascular disease (CVD) are age-related diseases. According to some studies, patients with CVD have a higher risk of bone loss. This retrospective study intended to reveal the correlation between osteoporosis and CVD in Chinese women. Although epidemiological evidence has provided evidence of the relationship between the two, it lacks clinical data in southeast China.

Methods: The 2873 participants completed the baseline survey from January 2007 to October 2019, and 2496 were included in this retrospective study. We divided all subjects into the osteoporosis group and the non-osteoporosis group based on their bone mineral density. Dual-energy x-ray absorptiometry (DXA) was used to examine bone mineral density. The general information came from the questionnaire survey and medical records.

Results: According to the criterion, the osteoporosis group had 799 subjects, with a mean age of 64.19 years. The non-osteoporosis group had 1697 subjects, with a mean age of 61.03 years. Subjects in the osteoporosis group had a significantly higher prevalence of hypertension and coronary heart disease. Besides, there was a higher probability of drinking tea and drinking milk in the osteoporosis group. In correlation analysis, the occurrence of osteoporosis correlated positively with hypertension and coronary heart disease. Logistic regression analysis showed that the odds of osteoporosis was high if participants had hypertension, coronary heart disease, or drank tea and drank milk.

Conclusions: This study indicated that patients with osteoporosis had a higher prevalence of CVD in Chinese women, and CVD is one of the hazard factors for osteoporosis.

Background

Osteoporosis is a skeletal disease accompanied by low bone mass and deterioration in bone microarchitecture, leading to increased bone fragility and risk of fractures [1]. Cardiovascular disease (CVD) is mainly caused by arteriosclerosis, including coronary heart disease, hypertension, cerebral infarction, and other vascular diseases. Osteoporosis and CVD are common clinical diseases. With the lifestyle changes and the aging of the population, the incidence has increased significantly and seriously threatens the physical and mental health of the elderly.

It was previously thought that the two were independent of each other, but epidemiological studies have proved the correlation between them [2, 3]. In recent years, with the further study of the relationship between osteoporosis and CVD, it has been confirmed that they have similar risk factors in the elderly, especially in postmenopausal women. Age, smoking, lack of physical exercise, vitamin D deficiency, and diabetes mellitus were considered the common risk factors for osteoporosis and CVD [4-6]. Some studies have indicated that patients with CVD have a higher risk of bone loss. Besides, individuals with low bone mass have higher mortality from CVD [7]. The possible link between CVD and osteoporosis urges us to analyze correlation and identify a common pathological basis. The similar pathogenesis of vascular

calcification and bone mineralization involves oxidative stress, inflammation, and lipid metabolism [8, 9]. In this process, they have common regulatory factors, such as bone morphogenetic proteins (BMP), osteoprotegerin (OPG), matrix protein Gla (MPG), and tumor necrosis factor-alpha (TNF-a) [10, 11].

Similarly, genetic research also provides evidence for the connection between the two. The deletion of specific genes in mice and mutation of critical genes in humans can lead to vascular calcification and early osteoporosis [12]. The research on the relationship between the two is beneficial to prevention and treatment. Specifically, the clinical evaluation of CVD patients should consider the measurement of bone mineral density. Also, patients with osteoporosis should undergo the examination of the electrocardiogram or Doppler ultrasound. This also has great significance in treating the two diseases [5].

Epidemiology provides the most direct and considerable evidence for the relationship. The different methods and populations that have been studied so far limit the reliability of the results [13]. Some clinical studies have been reported in some areas of China [14-16]. However, given the relatively small sample size included, it is difficult to reflect the overall situation. This retrospective study focuses on postmenopausal women in Fuzhou over 12 years, involving nearly three thousand participants, which can represent, to a certain extent, the prevalence of osteoporosis in southeastern China. It also provides extensive sample data for further investigating the relationship between osteoporosis and CVD in Chinese women.

Methods

Study Population

This retrospective study was carried out from January 2007 to October 2019 with participants from Fuzhou, capital of Fujian Province. All participants were investigated in the department of osteoporosis of the Fujian Academy of Chinese Medical Sciences. The 2873 participants accepted the questionnaire survey, and 2496 of them aged between 41 and 90 were included in this study. All subjects could provide complete medical records and sign informed consent independently.

The data required for the study came from the questionnaire survey. General information, such as age, height, weight, blood pressure, menarche age, menopausal age, past medical history, personal lifestyle, were collected and carefully filled in the unified form by the trained physicians. The height and weight were measured without shoes, and then the body mass index (BMI) was calculated.

All participants were excluded if they had hyperparathyroidism, diabetes, rheumatoid arthritis, and other endocrine and immune diseases that affect bone metabolism. Patients with severe liver and kidney and hematopoietic diseases and malignant tumors were also excluded. Further, none of the subjects had received osteoporosis treatment or other known drugs that affect bone metabolism. All potential subjects had complete data records. The written consent was necessary for all participants.

The diagnostic of osteoporosis was based on T score in the lumbar spine or femoral neck. T score £ -2.5 is osteoporosis; osteopenia is diagnosed as -2.5 < T score < -1.0; T score ³ -1.0 is normal [17]. All subjects were divided into the osteoporosis group and non-osteoporosis group according to their T score. Cardiovascular diseases were defined by asking participants at the first visit and checking relevant medical records if they had suffered from brain infarction, coronary heart disease, and hypertension. Lifestyle habits were defined as activities that participants perform every day.

Bone mineral density measurement

Dual-energy X-ray absorptiometry (DXA) (Discovery W, Hologic Inc, USA) was used to measure bone mineral density (BMD) of the lumbar spine and left femoral neck. The T score was calculated according to the reference range of the instrument manufacturer. The inspection was performed daily by the same professional physician. The coefficient of variation (CV) for repeated measurements is approximately 1.0%.

Statistical analysis

EpiDate 2 was used to enter and proofread data repeatedly, and SPSS 23.0(IBM, NY, USA) software was used to conduct all analyses. The results were expressed as average standard deviation or quantity (percentage). The *t*-test or Mann-Whitney U test was used for continuous variables. The chi-square test was used for the difference in frequency. Pearson or Spearman correlation analysis was used for univariate analyses of disease risk factors. Logistic regression analysis was confirmed with osteoporosis as dependent variables to evaluate the factors affecting osteoporosis. All the insignificant influencing factors were excluded from the analysis using the forward stepwise method. In all analyses, $P < 0.05$ suggested statistical significance.

Results

Characteristics of subjects between the osteoporosis group and non-osteoporosis group.

After excluding 377 participants who did not meet the criteria, 2496 subjects were included in the study. There were 799 people in the osteoporosis group and 1697 people in the non-osteoporosis group. The age of the osteoporosis group was between 47 and 85, with 64.19±6.68 years. The age of the non-osteoporosis group was between 41 and 85, with 61.03±6.82 years. Statistically, the age and menarche age of subjects who suffered from osteoporosis were significantly older than those who did not, and the menopause age was more advanced. They also had a lower height and lighter weight ($P < 0.001$). Besides, The BMD of the osteoporosis group was significantly lower than the non-osteoporosis group ($P < 0.001$) (Table 1).

Table 1 Characteristics of subjects between the osteoporosis group and non-osteoporosis group (mean ± SD)

	Total	Osteoporosis	Non-osteoporosis	*P*
N (%)	2496(100)	799(32.01)	1697(67.99)	NA
Age (years)	62.04±6.94	64.19±6.68	61.03±6.82	<0.001
Height (m)	1.56±0.05	1.55±0.05	1.57±0.05	<0.001
Weight (kg)	57.48±8.30	56.07±8.11	58.15±8.31	<0.001
BMI (kg/m^2)	23.60±3.06	23.29±3.04	23.46±2.99	0.014
Menarche age (years)	15.34±2.00	15.55±2.07	15.17±1.91	0.003
Menopause age (years)	49.72±4.14	49.87±3.98	50.27±3.93	0.007
Lumbar spine BMD (g/cm^2)	0.78±0.15	0.66±0.08	0.86±0.13	<0.001
Femoral neck BMD (g/cm^2)	0.73±0.14	0.64±0.13	0.74±0.11	<0.001

Abbreviations: *NA* not applicable, *BMI* body mass index, *BMD* bone mineral density, *SD* standard deviation

Comparison of influencing factors between the osteoporosis group and non-osteoporosis group.

Comparing the influencing factors between the two groups indicated that patients in the osteoporosis group had a higher prevalence of hypertension and coronary heart disease ($P < 0.05$). Besides, there was a higher probability of drinking tea and drinking milk in the osteoporosis group ($P < 0.05$) (Table 2).

Table 2 Comparison of influencing factors between the osteoporosis group and non-osteoporosis group (%)				
	Total	Osteoporosis	Non-osteoporosis	*P*
N, %	2496(100)	799(32.01)	1697(67.99)	NA
Smoking, *n* (%)	8(0.32)	2(0.25)	6(0.35)	0.670
Drinking coffee, *n* (%)	69(2.76)	29(3.63)	40(2.36)	0.070
Drinking tea, *n* (%)	246(9.86)	100(12.52)	146(8.60)	0.002
Drinking milk, *n* (%)	769(30.81)	321(40.18)	448(26.40)	<0.001
Hyperlipidemia, *n* (%)	74(2.96)	29(3.63)	45(2.65)	0.179
Hypertension, *n* (%)	442(17.71)	174(21.78)	268(15.79)	<0.001
Coronary heart disease, *n* (%)	120(4.81)	54(6.76)	66(3.89)	0.002
Cerebral infarction, *n* (%)	26(1.04)	11(1.38)	15(0.88)	0.258
Abbreviations: *NA*, not applicable				

Correlation analysis between different variables.

In correlation analysis, the occurrence of osteoporosis correlated positively with age, menarche age, drinking tea, drinking milk, hypertension, and coronary heart disease ($r > 0$, $P < 0.05$) but negatively with height, weight, BMI, and menopause age ($r < 0$, $P < 0.05$), whereas smoking, drinking coffee, hyperlipidemia, and cerebral infarction did not. The age, weight, BMI, drinking tea, drinking milk, and hyperlipidemia was positively related to hypertension ($r > 0$, $P < 0.05$), while the height and femoral neck BMD were negatively related to hypertension ($r < 0$, $P < 0.05$). Similarly, the femoral neck BMD was also negatively associated with coronary heart disease ($r < 0$, $P < 0.05$) while the age and menarche age were positively associated with coronary heart disease ($r > 0$, $P < 0.05$). The results also indicated that the risk of cerebral infarction increased with age. Besides, there were strong correlations between hypertension, coronary heart disease, and cerebral infarction ($r > 0$, $P < 0.01$) (Table 3).

Table 3 Correlation analysis between different variables

Variables	Osteoporosis (*n*)		Hypertension (*n*)		Coronary heart disease (*n*)		Cerebral infarction (*n*)	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age (years)	0.208**	<0.001	0.201**	<0.001	0.178**	<0.001	0.075**	<0.001
Height (m)	-0.148**	<0.001	-0.040*	0.043	-0.019	0.342	0.005	0.792
Weight (kg)	-0.125**	<0.001	0.084**	<0.001	0.017	0.385	0.009	0.671
BMI (kg/m^2)	-0.049*	0.014	0.131**	<0.001	0.037	0.067	0.005	0.799
Menarche age (years)	0.059**	0.003	-0.032	0.108	0.052**	0.009	0.002	0.937
Menopause age (years)	-0.057**	0.006	0.040	0.055	0.020	0.341	-0.010	0.630
Lumbar spine BMD (g/cm^2)	-0.703**	<0.001	0.017	0.400	-0.023	0.241	-0.012	0.549
Femoral neck BMD (g/cm^2)	-0.378**	<0.001	-0.208**	<0.001	-0.091**	<0.001	-0.012	0.553
Smoking (*n*)	-0.009	0.670	-0.026	0.189	-0.013	0.525	-0.006	0.776
Drinking coffee (*n*)	0.036	0.071	-0.001	0.943	-0.015	0.452	-0.017	0.397
Drinking tea (*n*)	0.061**	0.002	0.069**	0.001	0.026	0.192	-0.006	0.753
Drinking milk (*n*)	0.139**	<0.001	0.118**	<0.001	0.057**	0.004	0.037	0.061
Hyperlipidemia (*n*)	0.027	0.179	0.067**	0.001	0.027	0.178	0.030	0.136
Hypertension (*n*)	0.073**	<0.001	NA	NA	0.244**	<0.001	0.080**	<0.001
Coronary heart disease (*n*)	0.063**	0.002	0.244**	<0.001	NA	NA	0.090**	<0.001
Cerebral infarction (*n*)	0.017	0.390	0.080**	<0.001	0.090**	<0.001	NA	NA

Abbreviations: *r* Pearson or Spearman correlation coefficient, *BMI* body mass index, *BMD* bone mineral density, *NA* not applicable

*$P<0.05$; **$P<0.01$

Logistic regression analysis with osteoporosis as a dependent variable.

Taking osteoporosis as the dependent variable, we conducted a two-class logistic regression analysis. After adjusting the confounding factors such as age, height, weight, menarche age, menopause age, drinking tea, and drinking milk, the result showed that hypertension and coronary heart disease were significant influencing factors for osteoporosis ($P < 0.05$). The increased age, menarche age, and the occurrence of hypertension, coronary heart disease, drinking tea, drinking milk were related to the increased risk of osteoporosis. The adjusted OR of suffering from osteoporosis was1.280 for participants with hypertension compared to those without hypertension and 1.503 for participants when suffering from coronary heart disease. Moreover, lower height, lighter weight, and earlier menopause may also be related to the increased risk of osteoporosis (Table 4).

Table 4 Logistic regression analysis with osteoporosis as a dependent variable

Variables	β	SE	Wald	*P*	OR	95% C.I.
Age (year)	0.055	0.007	59.817	< 0.001	1.057	1.042-1.071
Height (m)	-2.826	0.985	8.238	0.004	0.059	0.009-0.408
Weight (kg)	-0.021	0.006	11.208	0.001	0.979	0.968-0.991
BMI (kg/m^2)	0.002	0.215	0.000	0.992	1.002	0.658-1.527
Menarche age (year)	0.049	0.023	4.810	0.028	1.051	1.005-1.098
Menopause age (year)	-0.026	0.011	6.035	0.014	0.974	0.954-0.995
Hypertension (*n*)	0.247	0.114	4.669	0.031	1.280	1.023-1.601
Coronary heart disease (*n*)	0.408	0.197	4.253	0.039	1.503	1.021-2.213
Cerebral infarction (*n*)	0.102	0.423	0.059	0.808	1.108	0.484-2.537
Hyperlipidemia (*n*)	0.238	0.246	0.933	0.334	1.269	0.783-2.056
Smoking (*n*)	-0.118	0.820	0.021	0.886	0.889	0.178-4.435
Drinking coffee (*n*)	0.245	0.258	0.902	0.342	1.278	0.771-2.118
Drinking tea (*n*)	0.278	0.126	4.879	0.027	1.320	1.032-1.689
Drinking milk (*n*)	0.571	0.092	38.095	< 0.001	1.769	1.476-2.121

Abbreviations: *BMI* body mass index, *β* correlation coefficient, *SE* standard error, *OR* odds ratio, *C.I.* confidence interval

Discussion

With the continuous extension of life expectancy, the incidence of CVD and osteoporosis is increasing. More evidence shows that there are common risk factors and similar pathological mechanisms between

the two [18]. In this retrospective study, we found that among all the women who met the criteria, there were 799 cases of osteoporosis, with a prevalence rate of 32.01%, which was similar to that reported in other literature [19, 20]. Among the 799 patients, 174 suffered from hypertension, and 54 suffered from coronary heart disease. The prevalence was significantly higher than that of non-osteoporosis. This illustrates that CVD may increase the risk of osteoporosis, which is consistent with previous studies [21-23]. In correlation analysis, advanced age, later menarche, earlier menopause, and lower height may also be associated with this risk. To further adjust the factors causing this increased risk, we conducted a multivariate regression analysis and found that hypertension and coronary heart disease were related to the increased risk of osteoporosis. This indicates a significant correlation between CVD and osteoporosis, and CVD is one of the hazard factors for osteoporosis, suggesting that fracture and CVD prevention should be considered in the clinic. According to the results, drinking tea and milk also increased the risk of osteoporosis, which was inconsistent with previous studies. This may be because we didn't record the duration and amount of drinking milk and tea.

Some studies have reported that low BMD, as a hazard factor for cardiovascular events, is superior to traditional risk factors in predicting disease development, such as hyperlipidemia and smoking [24, 25]. The lower BMD and increased bone loss rates were also related to an increased risk of CVD in the Chinese cohort [26]. Interestingly, a study showed a favorable relationship between reduced risk of cardiovascular disease and BMD [27]. Another study followed 6872 men and women for 5.7 years, and 196 developed myocardial infarction during this period. The result revealed that low hip BMD was a hazard factor for infarction [28]. In this study, we analyzed the influencing factors of CVD and found that age, weight, BMI, drinking tea, drinking milk, and hyperlipidemia were positively related to hypertension while the height and femoral neck BMD were negatively associated with hypertension. Similarly, the femoral neck BMD was also negatively correlated with coronary heart disease. This shows that low femoral neck BMD is one of the risk factors for CVD, which is consistent with the reported results.

Osteoporosis and CVD are common age-related diseases. As shown in the results, the risk of osteoporosis, hypertension, coronary heart disease, and cerebral infarction increased with age. Changes in estrogen levels caused by menopause or aging can directly affect blood vessel wall and bone metabolism [15]. Bones and blood vessels are considered to be important targets for estrogen. Estrogen can improve the function of endothelial cells and vascular smooth muscle cells, and inhibit platelet aggregation and the response of blood vessels to injury [29, 30]. Similarly, estrogen in serum can reduce the number and activity of osteoclasts and inhibit bone resorption. The decrease in estrogen results in increased bone resorption [31-33]. Besides, the reduction may lead to an increase in proinflammatory cytokines. The proinflammatory cytokines were related to bone loss and severe arteriosclerosis [34, 35].

As we know, oxidative stress increases with age, further leading to the production of oxidized lipids. The oxidative stress is involved in bone resorption by inducing osteoclast differentiation and inhibiting osteoblast differentiation and leads to vascular calcification because of the damage to endothelial cells [36-38]. Moreover, vascular endothelial cells may accelerate the differentiation of adipose stem cells into osteoblasts by secreting BMP [39]. Other matrix proteins are also found in bone tissue and vascular

matrix. Angiogenesis and bone formation can be coupled through unique vascular forms and pathways [40, 41]. The decrease in blood supply is easy to lead to atherosclerosis, which may affect blood circulation in bone and further damage bone metabolism, leading to osteoporosis [42]. The latest biological factors (sclerostin, fibroblast growth factor-23) are also related to atherosclerosis and bone metabolism [5]. These studies can explain the common pathological mechanism of age-related osteoporosis and CVD.

The limitation of this study is a single-center retrospective study with poor homogeneity, many confounding factors, and low evidence. Second, it is difficult to get the causal relationship between influencing factors and osteoporosis, so a prospective cohort study should be considered in the next step. Third, the information related to cardiovascular disease comes from medical records rather than immediate examination. Further research needs to be done based on this study.

Conclusion

In short, this observational study indicated the correlation between osteoporosis and cardiovascular disease in Chinese women. Based on the results, cardiovascular assessment should be considered in patients with osteoporosis to prevent adverse events. This further supports the view that there is a biological link between the two.

Abbreviations

CVD: cardiovascular disease; BMP: bone morphogenetic proteins; OPG: osteoprotegerin; MPG: matrix protein Gla; TNF-a: tumor necrosis factor-alpha; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; CV: coefficient of variation; NA: not applicable; BMI: body mass index; SD: standard deviation; SE: standard error; OR odds ratio; C.I.: confidence interval

Declarations

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Author contributions

HC drafted the manuscript. JL and LL were responsible for the questionnaire and medical records. YY assisted with bone density measurement. JG provided to the study conception and critical revision of the manuscript. The final version was reviewed and approved by all the authors.

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Availability of data and materials

The datasets generated during and analysed during the current study are not publicly available due to the protection of personal information but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All methods were carried out in accordance with the Declaration of Helsinki. This retrospective study performed using the date from questionnaire survey. All participants signed informed consent to obtain necessary personal information when receiving free BMD measurement. The Ethics approval is not required involving the epidemiological studies of pre-existing material and information according to the Measures for Ethical Review of Biomedical Research Involving People (National Health and Family Planning Commission of the People's Republic of China, http://www.gov.cn/gongbao/content/2017/content_5227817.htm) and the Ethics Committee of Clinical Research on Traditional Chinese Medicine of Fujian Academy of Chinese Medical sciences, http://fjszyy.com/kxyj_ny.php?classid=274&infoid=759.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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