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Association of bone mineral density with peripheral blood cell counts and hemoglobin in Chinese postmenopausal women

A retrospective study

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Abstract

Osteoporosis (OP) is a metabolic bone disease that can cause structural changes in bone marrow cavity. Bone marrow is the hematopoietic organ of adults. Accumulating evidence has shown a close connection between bone marrow hematopoietic function and bone formation. Some studies have revealed that OP is associated with hematopoiesis. However, the relationship is not definite.

This study aimed to evaluate the association between peripheral blood cell counts (white blood cells [WBC], red blood cells [RBC], platelets [PLT]), hemoglobin [HGB], and bone mineral density [BMD]) in a sample of Chinese postmenopausal women. This is a retrospective study involving 673 postmenopausal women cases. The BMD of lumbar spine and left hip joint were measured by dual-energy X-ray absorptiometry. The levels of blood cell counts and HGB were measured and analyzed.

The study results showed the WBC, RBC, PLT, and HGB levels of postmenopausal women in the OP group were all higher than those in the non-osteoporosis group. Spearman linear trend analysis and partial correlation analysis demonstrated that BMD was negatively correlated with WBC, RBC, PLT, and HGB in postmenopausal women.

Due to the differences between different countries and races, and there are few studies on the association of BMD with peripheral blood cell counts and HGB in Chinese Postmenopausal Women. Therefore, more large sample studies are needed.

Abbreviations: BM = bone marrow, BMD = bone mineral density, BMI = body mass index, HGB = hemoglobin, PLT = platelets, RBC = red blood cell, WBC = white blood cell.

Keywords: bone mineral density, hemoglobin, peripheral blood cell counts, postmenopausal women

1. Introduction

Postmenopausal osteoporosis (PMOP) refers to a metabolic osteopathy characterized by decreased overall bone mass, bone tissue microstructure destruction, and increased bone fragility and fracture susceptibility due to decreased ovarian function and decreased estrogen levels in women after menopause.[1] The imbalance of bone metabolism caused by the weakened bone formation and the increased bone resorption is an important cause of the incidence of osteoporosis (OP). The pathological changes mainly include the decrease of bone matrix and bone mineral content, the thinning of bone cortex, the decrease of the number and volume of bone trabecula, increased the volume of adipose tissue in bone marrow (BM) cavity, and decreased volume of hematopoietic tissue.[2,3]

BM is the major hematopoietic organ of adult mammals. It is an architecturally complex tissue that houses cells of the hematopoietic, endothelial lineages, and mesenchymal.[4] Adult BM also contains adipocytes, whose volume increases with aging and OP, and the number of which correlates inversely with the hematopoietic activity of the marrow.[5,6] Animal experiments showed that the bone mineral density (BMD) of ovariectomized (OVX) rats did not decreased significantly as compared with the corresponding Sham group at 4th week, but the volume of adipose tissue significantly increased. After the 8th week, compared with the Sham group, the BMD of OVX group decreased significantly, while the volume of hematopoietic tissue decreased and volume of adipose tissue increased, the number of megakaryocytes decreased, the number of osteoclasts and mast

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Written informed consent was obtained from each participating individual.

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The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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cells increased in BM section, thus, which indicated that when BMD of OVX rats decreased, BM hematopoietic function also decreased.[7] Besides, osteoblast (OB) and its precursor has been demonstrated to produce many of the cytokines and growth factors that play important roles in hematopoietic and myeloid development, including granulocyte colony-stimulating factor, interleukin-6, and transforming growth factor beta, and so on. And OB can directly affect red blood cells (RBC) production through erythropoietin.[8,9] It has been proved that conditional elimination of OB pedigree can lead to the loss of BM cells. Through the characterization of hematopoietic parameters of experimental mice, it was found that there were fewer lymphocytes, RBC, and myeloid progenitors in the BM, and the number of hematopoietic stem cells also decreased.[10] In addition to the obvious interrelationship between bone and hematopoietic tissue in animal models, it has also been observed in the clinic that patients with beta-thalassemia, chronic hemolysis, pernicious anemia, and sickle cell anemia often exhibit OP phenotype or low BMD.[11–16]

For the above-mentioned reasons and considering that different subgroups may have different susceptibility, we conducted a retrospective study to further explore the changes of BM hematopoietic function in OP patients. Therefore, the current study was carried out to investigate the association between peripheral blood cell counts (white blood cells [WBC], RBC, platelets [PLT]), hemoglobin (HGB), and BMD, which may reflect hematopoietic and osteogenic function, respectively.

2. Subjects and methods

2.1. Subjects

The data included a total of 673 cases of naturally postmenopausal women (ceased menstruation for at least 12 months) of Han nationality in Fuzhou area who were examined by the special department of osteoporosis of Fujian Academy of Traditional Chinese Medicine.

Inclusion criteria:

(1) Those who meet the diagnostic criteria of OP;
(2) The subjects were natural menopause;
(3) All subjects had informed consent and signed the informed consent voluntarily.

Exclusion criteria:

(1) Those who do not meet the diagnosis of OP;
(2) Rheumatoid arthritis, diabetes mellitus, hyperthyroidism, and other secondary OP;
(3) Those with serious cardiovascular and cerebrovascular diseases;
(4) Use drugs that may affect BMD, such as bisphosphonate, estrogen, androgen, and thyroid hormone.

This study was examined and approved by the Ethics Committee of Clinical Research of Traditional Chinese Medicine of Fujian Academy of Chinese Medical Sciences.

2.2. Research methods

Trained doctors conducted surveys using standardized questionnaires to collect data on lifestyle, health status, disease history and medication history, and recorded the general information of age, height, weight, and menopausal age of the subjects.

2.3. BMD measurement

The BMD of lumbar spine and left hip was measured by dual-energy X-ray absorptiometry (Hologic Discovery W Bone Densitometer, USA). All BMD measurements were performed by the same trained senior technologist and were accurately measured using acontrolled coefficient of variation 1.0CV%, accuracy 0.25%.

According to the BMD values of lumbar vertebrae (L1-L4) and left femoral neck, and referring to the Osteoporosis Committee of China Gerontological Society, it is recommended to use 2 standard deviations below the peak bone mass (−2.0SD) or 25% reduction in bone mass as the diagnostic criteria for OP in Chinese people,[17] which were divided into the OP group ($T \leq -2.0$) 399 cases and non-osteoporosis (NOP) group ($T > -2.0$) 274 cases.

2.4. Height and weight measurement

The height and weight of all subjects were measured by the same technician.

During height measurement, the subjects take off shoes and stand on the height measuring instrument, with head, buttocks, and ankles resting on the height measuring instrument at 3 points. The reading at the intersection of the highest point of the head and the vertical line of the column of the height measuring instrument is the height reading, which is expressed in meters.

During the weight measurement, the subjects take off shoes and stand on the base of the weight measuring instrument in single clothes. The position shall be correct and the body shall be straight. The needle reading on the weight measuring instrument shall be observed and the value is expressed in kilograms.

2.5. Determining the levels of peripheral blood cell counts and HGB

The peripheral blood cell counts and HGB level of all subjects were measured with 5 ml of forearm venous blood after a night of fasting (≥12 hours) by SYSMEX XN3000 automatic blood analyzer and TOSHIBA-120FR.

2.6. Statistical methods

SPSS 20.0 statistical software was used for analysis. Measurement data are expressed as mean ± standard deviation. The specific statistical methods involved are rank sum test, Spearman linear analysis, partial correlation analysis, and multiple stepwise regression analysis. $P < .05$ indicated that the difference was statistically significant.

3. Results

3.1. General information

Among the 673 postmenopausal women included in the study, OP accounted for 59.3% and NOP accounted for 40.7%. First, the general data of different groups were compared, and the results showed that there were differences in age, duration of menopause, height, and weight between OP group and NOP group ($P < .01$). The height and weight of OP group were lower than that of NOP group. This is consistent with one of the clinical symptoms of OP: OP patients may have shortened height or hunchback. Although there was no statistical difference in body

Table 1

Comparison of the general information of postmenopausal women between groups.

	OP Group (399 cases)	NOP Group (274 cases)	*P*-value
Age (yr)	63.57 ± 6.08	62.00 ± 6.11	.001
Duration of menopause (yr)	13.39 ± 7.22	11.87 ± 7.33	.005
Height (m)	1.55 ± 0.05	1.57 ± 0.05	<.001
Weight (kg)	57.11 ± 7.73	59.40 ± 9.33	.009
BMI (kg/m^2)	23.76 ± 3.04	24.14 ± 3.30	.479
WBC (*10^9/L)	5.36 ± 1.44	5.05 ± 1.03	.023
RBC (*10^12/L)	4.27 ± 0.50	4.06 ± 0.43	<.001
HGB (g/L)	129.14 ± 15.68	121.79 ± 13.35	<.001
PLT (*10^9/L)	217.51 ± 56.06	195.35 ± 55.94	<.001
ALT (U/L)	20.55 ± 9.37	20.23 ± 8.05	.992
AST (U/L)	21.58 ± 8.29	22.28 ± 6.51	.042
CREA (umol/L)	65.04 ± 11.59	64.49 ± 10.99	.866
BUN (mmol/L)	5.32 ± 1.11	5.35 ± 0.94	.754

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BUN = blood urea nitrogen, CREA = creatinine, HGB = hemoglobin, PLT = platelets, RBC = red blood cell, WBC = white blood cell.

mass index (BMI) between 2 groups, according to the BMI reference standard for Chinese, the obesity (BMI ≥ 27 kg/m^2) in the OP group accounted for 14.3% (57 out of 399 cases) less than that in the NOP group (16.8%: 46 out of 274 cases). This is consistent with the conclusion that BMI increases with BMD in postmenopausal OP women,[18] obesity is positively associated with BMD and negatively correlated with OP.[19] And the results of comparison of peripheral blood cell counts and HGB in OP group and NOP group showed that WBC ($P = .023$), RBC, PLT, and HGB ($P < .001$) in OP group were all higher than those in NOP group (Table 1).

3.2. The correlation of BMD to peripheral blood cell counts and to HGB

Overall, BMD of the lumbar vertebrae was negatively correlated with RBC ($P < .05$), HGB ($r = -0.088$, $P = .059$), and PLT ($r = -0.090$, $P = .054$). BMD of the left femoral neck was negatively correlated with WBC, RBC, HGB, and PLT ($P < .01$). As a result, WBC, RBC, HGB, and PLT increased with the decrease of BMD (Table 2).

And simple linear analysis showed that age, duration of menopause, height, weight, and BMI were correlated with BMD of lumbar spine and femoral neck. In order to exclude the influence of these factors on BMD, the 5 variables were used as control variables, further partial correlation analysis was made between WBC, RBC, HGB, PLT, and BMD of lumbar spine and femoral neck. The results showed that BMD of lumbar spine was negatively correlated with RBC, HGB ($P < .01$), PLT ($r_s = -0.085$, $P = .069$), BMD of left femoral neck was negatively correlated with WBC ($P < .05$), RBC, HGB, and PLT ($P < .01$) (Table 3).

3.3. HGB and RBC were elevated in OP patients

We conducted multivariate stepwise regression analysis of BMD of lumbar spine and femoral neck with multivariate, and found that lumbar BMD was affected by age ($P = .022$), height ($P < .001$), weight ($P = .005$), BMI ($P = .010$), HGB ($P = .003$). BMD of the left femoral neck was affected by age, RBC, and BMI ($P < .001$) (Table 4).

The influence of other variables on BMD was negligible (see Table, http://links.lww.com/MD/E447, Supplemental Content, which illustrates other variables have no effect on BMD).

3.4. The correlation of BMD to liver function and to kidney function

The correlation between alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen, and BMD was also analyzed, but no correlation was found. Previous studies have shown that OP is a common skeletal complication in patients with chronic liver disease,[20,21] and a cross-sectional study in Korea shows that there is a negative correlation between liver enzyme level and BMD, and there is a significant correlation between OP/BMD reduction and liver disease.[22] This is inconsistent with our results and may require further study (Table 5).

4. Discussion

Our results do not demonstrate an increased incidence of anemia in Chinese PMOP patients. On the contrary, in this study, OP patients showed higher peripheral blood cell counts, HGB levels

Table 2

Spearman analysis of bone mineral density of lumbar spine and femoral neck with influencing factors.

	WBC		RBC		HGB		PLT	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Lumbar vertebrae	−0.069	.140	−0.107	.021	−0.088	.059	−0.090	.054
Left femoral neck	−0.152	.001	−0.232	<.001	−0.168	<.001	−0.153	.001

HGB = hemoglobin, PLT = platelets, RBC = red blood cell, WBC = white blood cell.

Table 3

Partial correlation analysis of bone mineral density of lumbar spine and femoral neck with influencing factors.

	WBC		RBC		HGB		PLT	
	r_s	*P*	r_s	*P*	r_s	*P*	r_s	*P*
Lumbar vertebrae	−0.048	.302	−0.138	.003	−0.141	.002	−0.085	.069
Left femoral neck	−0.110	.019	−0.254	<.001	−0.167	<.001	−0.144	.002

HGB = hemoglobin, PLT = platelets, RBC = red blood cell, WBC = white blood cell.

Table 4

Multiple stepwise regression analysis of bone mineral density of lumbar spine and femoral neck with influencing factors.

	B	SE	Beta	*t*	*P*	95% CI
Lumbar vertebrae	3.911	1.273		3.072	.002	1.409, 6.413
Age (yr)	−1.876	0.814	−0.792	−2.304	.022	−3.475, −0.276
Height (m)	−0.003	0.001	−0.165	−3.516	<.001	−0.005, −0.001
HGB (g/L)	−0.001	0.000	−0.137	−3.025	.003	−0.002, 0.000
Weight (kg)	0.030	0.011	2.014	2.793	.005	0.009, 0.051
BMI (kg/m^2)	−0.068	0.026	−1.725	−2.601	.010	−0.120, −0.017
Left femoral neck	1.546	0.091		16.921	<.001	1.367, 1.726
Age (yr)	−0.006	0.001	−0.278	−6.295	<.001	−0.008, −0.004
RBC (*10^12/L)	−0.071	0.012	−0.258	−5.853	<.001	−0.094, −0.047
BMI (kg/m^2)	−0.006	0.002	−0.155	−3.577	<.001	−0.010, −0.003

BMI = body mass index, HGB = hemoglobin, RBC = red blood cell.

than NOP patients. Multiple stepwise regression analysis showed that lumbar spine BMD was affected by age, height, weight, BMI, HGB. BMD of the left femoral neck was affected by age, RBC, and BMI. Correlation analysis showed that BMD was negatively correlated with peripheral blood cell counts and HGB in postmenopausal women.

This is inconsistent with the existing clinical findings: A study of healthy postmenopausal women from Seoul, Korea,[23] showed a positive relationship between blood cell counts and BMD in postmenopausal women, and the study results also suggest that blood cell counts could be a putative marker for estimating BMD in postmenopausal women. This is consistent with the conclusion of a study of 371 postmenopausal women (82 anemic patients) from Turkey: Anaemia as a risk factor for low BMD in postmenopausal women.[24] However, a prospective longitudinal study based on cardiovascular health concluded that there was no correlation between the decrease of HGB level and BMD, and neither a single HGB measurement nor longitudinal change in HGB would be useful as a marker of low BMD in the short-term.[25] Therefore, the clinical utility of these studies remains to be seen.

According to our results, we hypothesized that PMOP patients with the decrease of BM trabecular structure and increased adipose tissue volume, which may not negatively regulate hematopoietic function. Through literature review, it is found that the current researches are consistent with our conjecture: An important physiological function of BM adipose tissue may to provide an expandable/contractile fat depot, which is critical to minimize the energy required to sustain optimal hematopoiesis.[26] Animal experiments show that BM adipocytes promote stem cell regeneration and hematopoiesis by secreting stem cell factors. Adipogenesis is likely a faster way of increasing the production of hematopoietic stem cell niche factors as compared to the construction of new perivascular niches.[27] In addition, a work based on studying primary human BM adipocytes isolated from hip surgery patients at the molecular level, through microarray analysis, and at the functional level, by assessing their relationship with primary human hematopoietic stem cells by the long-term culture initiating cell assay. It was found that BM adipocytes play a supporting role in the hematopoietic niche and directly sustain hematopoietic stem cells survival.[28]

In addition to the above research hypothesis and the conclusions of related literatures. We also found an interesting and contradictory point: it has been proved that the decreased level of estrogen (estrogen is an antioxidant) in postmenopausal women leads to the weakened function of tissue antioxidant system, which eventually leads to the loss of bone mass and the abnormality of bone metabolism[29–31]; moreover, obesity and oxidative stress are linked, with higher (Free Oxygen Radical Testing - reactive oxygen species levels) values and lower (Free Oxygen Radical Defence - antioxidant capacity value) values in obese patients[32]; with the influence of oxidative stress, the level of reactive oxygen species in OBs increased, which led to the dysfunction of cell function, decreased proliferation ability and eventually apoptosis.[33] These conclusions are obviously inconsistent with obesity is positively associated with BMD and negatively correlated with OP. And according to the BMI reference standard for Chinese, in this study, although the obesity (BMI ≥27 kg/m^2) in the OP group accounted for 14.3% (57 out of 399 cases) less than that in the NOP group (16.8%: 46 out of 274 cases), the overweight (BMI ≥24 kg/m^2) in the OP group accounted for 47.1% (188 out of 399 cases) more than that in the NOP group (46.7%: 128 out of 274 cases). It seems difficult to get a definite axis of relationship from these conclusions. Considering that the pathogenic factors of OP are not single and each factor affects each other, more samples and experiments may be needed for research and analysis.

There are some limitations in this study. First, the data sources of this study have regional limitations; secondly, the results may be affected by a variety of factors: sample size, race, age, measurement, and location of BMD and statistical methods. Nevertheless, this study has important advantages. The report

Table 5

Spearman correlation coefficient to analyze the correlation between bone mineral density and liver, kidney function.

	ALT		AST		BUN		CREA	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Lumbar vertebrae	0.004	.923	0.078	.086	−0.028	.576	−0.064	.155
Left femoral neck	−0.018	.685	−0.069	.129	0.080	.112	0.063	.161

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CREA = creatinine, BUN = blood urea nitrogen.

does not support the widely reported view that the volume of BM adipocytes increases with age and the development of OP, which leads to the decrease of BM hematopoietic tissue and the decrease of hematopoietic capacity, which can be used as the direction of future research. In the future, we can include more cases and strengthen the basic experimental research, which has clarified our research point.

5. Conclusions

Our results showed that the HGB and blood cell counts in the OP group of postmenopausal women were higher than those in the NOP group, and with the decrease of BMD, HGB, and blood cell counts increased. This is different from other studies. In the future, HGB and peripheral blood cell counts can be used as detection or screening markers of PMOP to study the relationship between them and BMD, so as to clarify the effect of OP on hematopoietic function of BM.

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