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Original Research Article

Correlation between breast cancer and osteocalcin levels, and risk of hypertension in postmenopausal women: Implications for pharmacological intervention

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Abstract

Purpose: *To investigate the correlation between breast cancer (BC), osteocalcin (OC) and hypertension risk in postmenopausal women.*
Methods: *Two hundred patients with BC and 200 non–BC women who visited The First People's Hospital of Wenling Hospital, Wenling, China from June 2018 to March 2021 were included in the study. Fifty-three patients with hypertension and 157 non-hypertensive patients were included in the hypertension studies. The enrolled postmenopausal women were divided into control, BC, hypertensive and non–hypertensive groups and risk factors for hypertension were analyzed. Pearson's correlation coefficient was performed to correlate OC levels with clinical indices. The incidence of hypertension in each group was counted and its correlation with OC levels was determined using Chi–square test.*
Results: *Age, BMI, OC, SBP, DBP, TC, TG, PTH and FPG levels were risk factors for the progression of hypertension in postmenopausal women ($OR > 1$, $p < 0.05$). Serum levels of OC in postmenopausal women had negative correlation with age, BMI, SBP, DBP, TC, TG, PTH, 25–(OH)D3 and FPG levels ($r < 0$, $p < 0.05$), but had positive correlation with HDL–C, CTX and PINP levels ($r > 0$, $p < 0.05$). With the elevation of OC levels, the incidence of hypertension showed a decreasing trend in postmenopausal women ($p < 0.05$).*
Conclusion: *Menopause is a risk factor for BC in women, while low OC levels are significantly related to elevated risk of hypertension in postmenopausal women. These findings suggest that pharmacological intervention to increase OC levels may have potential benefits in mitigating the risk of hypertension in postmenopausal women.*

Keywords: *Breast cancer, Hypertension, Menopause, Osteocalcin*

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INTRODUCTION

Breast cancer (BC) is classified as carcinoma and sarcoma. Carcinoma refers to a cancer occurring in the epithelial component of the breast, while sarcoma is a rare type of cancer occurring in the stromal (connective tissue) component of the breast. The incidence of BC is

now ranked first among all malignant tumors in women [1,2]. The onset of BC is subtle and as it progresses, it metastasizes to many organs and damages normal tissues [3]. Therefore, risk factors for BC should be examined to determine biological markers of pathogenesis. Postmenopausal women are a high–risk group for cervical, breast and vaginal diseases [4,5] due to autonomic dysfunction, a decline in ovarian function and decreased or lack of estrogen. It was found that the progression of BC in postmenopausal women is often caused by dysregulation of endogenous estrogen, but the exact mechanisms still need further elucidation [6].

Osteoporosis and bone loss caused by reduced estrogen levels and the inhibition of the reproductive axis have become major health problems for postmenopausal women [7]. Osteocalcin (OC), a non–collagenous protein, is synthesized and secreted by osteoblasts, which regulates the metabolism of bone and blood lipid, glucose and insulin levels, and is a sensitive and specific biochemical marker reflecting bone metabolism and bone remodeling. Moreover, OC promotes fat burning and consumption by liver and muscle tissues through the regulation of the lipocalin signaling pathway [8,9]. In a previous study, it was shown that serum OC is a protective factor for hypertension, hyperglycemia and hyperlipidemia, and that higher levels of OC may help prevent or delay metabolic syndrome (MS) [10]. In addition, circulating undercarboxylated OC has been demonstrated as an independent factor for carotid calcification in patients with primary hypertension and it may also serve as a crucial biomarker for carotid calcification [11]. Currently, much of the focus of clinical research has been on the association of OC levels with diseases such as diabetes mellitus and multiple sclerosis (MS), while a few studies have investigated the correlations between OC levels and hypertensive diseases in postmenopausal women.

This research first analyzed the risk of BC in postmenopausal women and thereafter examined the correlations of serum OC levels with the risk of hypertension.

METHODS

Clinical data

Two hundred (200) BC patients, who visited The First People's Hospital of Wenling Hospital from June 2018 to March 2021, were included as study group. Another 200 non–BC women during the same period were chosen as control group. They voluntarily signed informed consent; no previous history of malignancy; no positive findings in both breasts by physical examination and adjuvant examinations such as mammography and MRI. The research was approved by the Ethics Committee of The First People's Hospital of Wenling (approval no. KY–2017–2012–21) and carried out in conformity with the Declaration of Helsinki [12].

Inclusion criteria

Patients were included based on the Guidelines and Standards for the Diagnosis and Treatment of Breast Cancer of Chinese Anti–Cancer Association (2015 Edition) [13] and BC (*in situ* and invasive cancer) was confirmed by paraffin pathological examination; age (18 – 80 years); sex (female); and voluntarily signed an informed consent form.

Exclusion criteria

Patients who met the following criteria were excluded: concomitant endocrine system disorders such as parathyroid disease, thyroid disease, hypercortisolism, etc.; comorbidity with severe hepatic, renal and pulmonary insufficiency; recent stressful events such as surgery; recent administration of anti–osteoporosis drugs such as vitamin D, estrogen receptor modulators, calcium tablets, bisphosphonates, calcitonin, etc; recent treatment with antihypertensive drugs; recent use of drugs affecting bone metabolism such as estrogens and glucocorticoids; history of fracture within the last 2 years; combination of other malignancies; pregnancy or lactation.

Hypertensive postmenopausal women

Two hundred and ten postmenopausal women were recruited for this study. One hundred and fifty-seven women (157) were allocated to the hypertensive group and fifty-three (53) women to the non–hypertensive group based on whether they had hypertension.

Questionnaire

A questionnaire was designed according to the purpose of this study which included age, body mass index (BMI), menopausal state and menopausal age, history of postmenopausal hormone replacement therapy, duration of breastfeeding, menstrual cycle, number of live births, age of the first live birth, history of oral contraceptives/abortion/smoking, family history of hypertension/diabetes, history of biopsy for benign breast diseases, and age at menarche.

Laboratory tests

Fasting venous blood (5 mL) of each subject was collected and centrifuged for 5 minutes at 3000 rpm (R = 6 cm). The supernatant was stored in a - 80 °C refrigerator.

Bone metabolism index

Serum osteocalcin (OC), C–terminal telopeptide of type I collagen (CTX), 25–hydroxyvitamin D3 (25 – $(OH)D_3$), parathyroid hormone (PTH) and Procollagen type II N–terminal propeptide (PINP) levels were assayed by electrochemiluminescence (Shenzhen Antibiotech Co.) and automatic electrochemiluminescence analyzer (Cobas E601, Roche Diagnostics Co. Ltd.).

OC locus determination criteria

Osteocalcin (OC) levels at the first quartile, Q1, (25 % locus) was ≤ 16.62 ng/mL; Q2 (25 – 50 % locus) was 16.63 – 20.54 ng/mL; Q3 (50 – 75 %) locus was 20.55 – 25.42 ng/mL; Q4 (75 % locus) was ≥ 25.43 ng/mL.

Lipid and glucose levels

Total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG) levels, low–density lipoprotein cholesterol (LDL–C) and high–density lipoprotein cholesterol (HDL–C) were determined utilizing a fully automated biochemical analyzer (Atellica CH930, Shanghai Jumu Medical Devices Co.).

Blood pressure

After sitting still for > 5 minutes, blood pressure measurement was conducted with the patient in sitting position. Three consecutive measurements were taken using a fully automated electronic blood pressure monitor (UDEX – Twin II, Shanghai Hanfei Medical Equipment Co., Ltd.) and the average reading was recorded. Hypertension was determined based on the standard of diagnosis in the Guidelines for the Prevention and Treatment of Hypertension in China (2018 Revised Edition) [14], namely: normal high value (diastolic blood pressure (DBP): 80–89 mmHg and/or systolic blood pressure (SBP): 120–139 mmHg), while hypertension (DBP ≥ 90 mmHg and/or SBP ≥ 140 mmHg).

Quality control

The questionnaires, training, physical examination, blood specimen collection, specimen storage, transportation and testing were implemented based on the standards and operational specifications established by the project center. All staff received a one-week training and were certified before the commencement of study. Data was entered online by two independent researchers.

Statistical analysis

Statistical Package for Social Sciences (SPSS; IBM, Armonk, USA) version 24.0 was adopted. Measurement data were represented as mean ± standard deviation (SD) and determined by *t*-test. Count data were represented by rates and examined by χ^2 test. Linear correlations were tested using χ^2 test while Pearson test was used for correlation analysis. Univariate analysis was implemented to primarily screen the factors affecting the occurrence of BC, multi-factors were analyzed using a logistic model with a = 0.05, and $p < 0.05$ was deemed as statistically significant.

RESULTS

Factors affecting the occurrence of BC

Both groups exhibited no significant differences in age, menopausal age, duration of lactation, menstrual cycle, number of live births, age of the first live birth, history of postmenopausal hormone replacement therapy, history of lactation/oral contraceptives/live births/miscarriage/smoking ($p > 0.05$). Conversely, both groups had marked differences in BMI, age at menarche, menopausal state and history of biopsy for benign breast diseases ($p < 0.05$; Table 1).

Factors affecting the occurrence of BC

According to unconditional logistic regression analysis, history of biopsy for benign breast diseases, BMI ≥ 24 kg/m^2, age at menarche ≥ 14 years old and menopause may be risk factors influencing the occurrence of BC (*OR* > 1, $p < 0.05$; Table 2).

Factors affecting the development of hypertension

From the results in Table 3, the hypertensive group exhibited higher age, BMI, SBP, DBP, TC, TG, PTH, 25-$(OH)D_3$ and FPG levels and lower OC, HDL-C, CTX and PINP levels than the non–hypertensive group ($p < 0.05$);

Table 1: Univariate analysis of factors affecting the occurrence of BC (n = 200)

Item		Control group	Study group	Statistical values	*P*–value
Age (years)		51.25±4.98	51.03±5.11	0.436	0.663
Menopausal age (years)		49.02±3.36	48.93±4.05	0.242	0.809
Duration of breastfeeding (months)		13.26±2.59	13.29±2.71	0.113	0.910
Menstrual cycle (d)		29.65±3.37	30.09±2.76	1.429	0.154
Number of live births (times)		1.89±0.28	1.87±0.25	0.754	0.451
Age of the first live birth (years)		25.26±2.75	25.06±3.16	0.675	0.500
History of postmenopausal hormone replacement therapy		4 (2.00)	9 (4.50)	1.988	0.159
Lactation history		167 (83.50)	171 (85.50)	0.305	0.581
History of oral contraceptive consumption		39 (19.50)	45 (22.50)	0.542	0.461
History of live births		188 (94.00)	182 (91.00)	1.297	0.255
History of miscarriage		94 (47.00)	90 (45.00)	0.161	0.688
Smoking history		23 (11.50)	27 (13.50)	0.366	0.545
History of biopsy for benign breast diseases		16 (8.00)	41 (20.50)	13.170	0.000
BMI (kg/m^2)	< 24	141 (70.50)	102 (51.00)	16.076	0.000
	≥ 24	59 (29.50)	98 (49.00)		
Age at menarche (years)	< 14	101 (50.50)	77 (38.50)	5.846	0.016
	≥ 14	99 (49.50)	123 (61.50)		
Menopausal state	No	116 (58.00)	74 (37.00)	17.684	0.000
	Yes	84 (42.00)	126 (63.00)		

Table 2: Multifactorial analysis of factors affecting the occurrence of BC

Factor	B	Standard error	*Wald*	*P*–value	*OR*	95% CI
History of biopsy for benign breast disease	1.087	0.314	11.982	0.001	2.965	1.602–5.488
BMI (≥ 24 kg/m^2)	0.831	0.210	15.685	0.000	2.296	1.522–3.465
Age at menarche (≥ 14 years)	0.488	0.203	5.801	0.016	1.630	1.095–2.425
Menopausal status (Yes)	0.855	0.205	17.415	0.000	2.351	1.574–3.513

Table 3: Univariate analysis of factors affecting the occurrence of hypertension in postmenopausal women

Item	Non–hypertensive group (n = 157)	Hypertensive group (n = 53)	Statistical values	*P*–value
Age (years)	47.26±3.95	53.06±4.92	8.665	0.000
BMI (kg/m^2)	22.95±1.27	25.29±2.28	9.299	0.000
OC (ng/mL)	22.06±4.02	18.02±3.35	6.582	0.000
SBP (mmHg)	126.82±11.26	159.23±13.02	17.400	0.000
DBP (mmHg)	82.65±10.25	102.08±6.13	13.024	0.000
TC (mmol/L)	5.62±0.86	6.35±1.21	4.789	0.000
TG (mmol/L)	1.26±0.35	2.34±0.49	17.443	0.000
HDL–C (mmol/L)	1.59±0.43	1.03±0.19	9.172	0.000
LDL–C (mmol/L)	3.46±0.59	3.52±0.61	0.635	0.526
PTH (ng/mL)	41.03±3.26	45.56±2.76	9.074	0.000
25–(OH)D_3 (pg/mL)	31.46±4.19	50.91±5.25	27.337	0.000
CTX (ng/mL)	0.49±0.12	0.35±0.09	7.782	0.000
PINP (ng/mL)	58.25±5.16	55.59±4.97	3.275	0.001
FPG (mmol/L)	5.07±1.58	6.14±1.02	4.612	0.000
Family history of hypertension	16 (10.19)	6 (11.32)	0.054	0.816
Family history of diabetes	13 (8.28)	4 (7.55)	0.029	0.866

Table 4: Logistic multifactorial analysis of risk factors for hypertension in postmenopausal women

Factor	*B*	Standard error	*Wald*	*P*–value	*OR*	95% CI
Constant	–2.828	0.736	14.785	0.000	0.059	–
Age	2.590	0.747	12.017	0.001	13.333	3.083–57.673
BMI	2.839	0.834	11.592	0.001	17.100	3.336–87.655
OC	2.540	0.383	44.036	0.000	8.673	5.986–20.831
SBP	2.007	0.728	7.600	0.006	7.439	1.78–30.980
DBP	2.325	0.823	7.990	0.005	10.227	2.040–51.275
TC	1.299	0.299	18.868	0.000	3.667	2.040–6.590
TG	0.925	0.132	49.029	0.000	2.522	1.946–3.267
HDL–C	0.444	0.131	2.165	0.129	1.559	1.206–2.016
PTH	1.665	0.147	129.066	0.000	5.285	3.965–7.043
25– $(OH)D_3$	0.279	0.284	5.065	0.067	3.592	2.058–6.269
CTX	1.736	0.294	3.254	0.102	5.677	3.193–10.093
PINP	0.711	0.324	4.809	0.052	1.456	1.260–1.927
FPG	1.025	0.326	9.883	0.002	2.788	1.471–5.284

Table 5: Correlation between serum OC levels and clinical indicators in postmenopausal women

Coefficient	Age	BMI	SBP	DBP	TC	TG	HDL–C	PTH	25-$(OH)D_3$	CTX	PINP	FPG
R	-0.365	-0.562	-0.613	-0.662	-0.395	-0.411	0.356	-0.422	-5.825	0.435	0.577	0.421
P–value	0.019	0.000	0.000	0.000	0.015	0.09	0.020	0.05	0.000	0.05	0.000	0.06

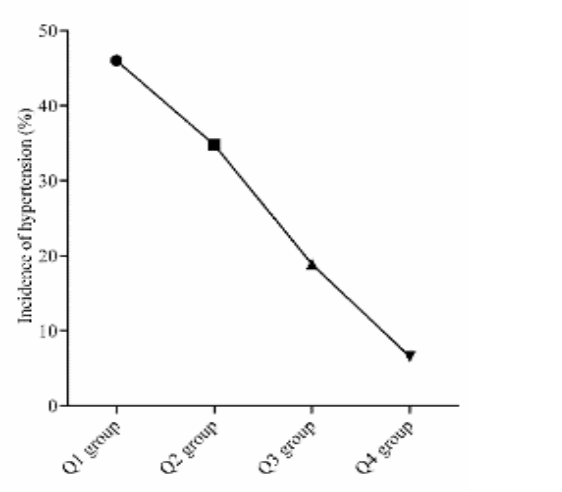

Figure 1: Comparison of the incidence of hypertension in postmenopausal women with different OC levels. Q1 – Q4 groups: Osteocalcin (OC) levels at the first to fourth quartiles (Q1: ≤ 16.62 ng/mL; Q2: 16.63 – 20.54 ng/mL; Q3: 20.55 – 25.42 ng/mL; Q4: ≥ 25.43 ng/mL)

LDL-C and family history of hypertension/diabetes mellitus showed no significant differences between the hypertensive and non–hypertensive groups ($p > 0.05$).

Risk factors of hypertension

According to unconditional logistic regression analysis, age, BMI, OC, SBP, DBP, TC, TG, PTH, and FPG levels may be risk factors for the progression of hypertension in postmenopausal women ($OR > 1$, $p < 0.05$; Table 4).

Correlation analysis

Pearson correlation showed that serum OC levels in postmenopausal women showed negative correlation with age, BMI, SBP, DBP, TC, TG, PTH, 25–$(OH)D_3$ and FPG levels ($r < 0$, $p < 0.05$), and exhibited positive correlation with HDL–C, CTX and PINP levels ($r > 0$, $p < 0.05$) (Table 5).

Incidence of hypertension in postmenopausal women with different OC levels

Comparison of the incidence of hypertension in postmenopausal with different osteocalcin (OC) levels is shown in Figure 1. With the increase in OC levels, the incidence of hypertension showed a decreasing trend in postmenopausal women ($p < 0.05$ Figure 1).

DISCUSSION

Epidemiological studies have found that there are many predisposing factors to BC, such as hormone levels, genetic factors, lactation history, immune factors and menopausal status [15]. In a meta–analysis, it has been pointed out that menarche and menopause represent the beginning and end of reproductive-related ovarian activity, respectively, and influence the risk of BC. Abu–Bedair *et al* [16] demonstrated that the risk of BC in postmenopausal women was positively associated with testosterone levels. In another study, Dibaba *et al* [17] showed that menopause is a risk factor for increased BC mortality. The results of this study indicate that a

history of biopsy of benign breast disease, BMI ≥ 24 kg/m^2, age at menarche ≥ 14 years old and menopause may be risk factors for the development of BC, with menopausal women showing a 2.351 times elevated risk of BC. This is consistent with the results of the above–mentioned studies. The reason may be that BC is sensitive to hormones, and sex hormones are particularly crucial in the development of BC, among which estrogen acts on breast cells through the toxicity of its metabolites and the receptor signaling pathway, accelerating the development of tumor cells and malignant transformation. Progesterone inhibits the pro–proliferative effect of estrogen on breast epithelial cells, and androgens enhance the risk of BC by directly or indirectly facilitating the growth of BC. The decrease or cessation of sex hormone secretion, such as progesterone and estrogen, in postmenopausal women causes changes in the activity of the hypothalamic–pituitary–ovarian axis, inducing proliferation of the mammary epithelium and therefore increasing the risk of BC [18,19]. The decrease in estrogen levels in postmenopausal women results in a loss in cardiovascular protective effect of estrogen, thereby increasing the risk of cardiovascular diseases (coronary heart disease, hypertension, etc.). Therefore, it is critical to explore a sensitive marker to predict the progression of hypertension in postmenopausal women. It has been shown that hypertension has close association with osteoporosis, as hypertensive patients have decreased levels of ionized calcium, increased daily urine, calcium excretion and secondary hypersecretion of PTH levels. This enhances intestinal calcium and bone resorption, resulting in a "migration" of blood calcium levels and decreased bone calcium, which induces osteoporosis [20]. Therefore, it is speculated that changes in bone metabolic markers may also be associated with hypertension [21]. Osteocalcin is utilized to assess bone metabolism, bone formation and bone turnover rate, and participates in the modulation of glucolipid metabolism and energy metabolism [20]. In an animal study, Brennan-Speranza *et al*. pointed out that OC-deficient mice had severely disordered metabolic phenotype with abnormal fat deposition, low energy expenditure, poor glucose tolerance and insulin resistance, and that upregulation of OC expression reduced serum TG levels and regulated insulin sensitivity [22]. Furthermore, serum OC negatively regulates and inhibits atherosclerosis [23]. In this study, the correlation of bone metabolic markers with hypertension in postmenopausal women was analyzed, with the aim being to identify bone metabolic markers that may predict the occurrence of hypertension. Results show that OC levels were lower in the hypertensive group (18.02 ± 3.35) ng/mL than in the non–hypertensive group (22.06 ± 4.02 ng/mL). In addition, OC levels were closely related to age, BMI, SBP, DBP, and other indicators in postmenopausal women. Previously, Xu *et al* reported that serum OC levels were higher in female hypertensive patients (10.80 ± 6.29 μg/L) compared to healthy individuals, and OC levels in male hypertensive patients (6.57 ± 3.49 μg/L) showed no significant differences compared to healthy individuals [24], which is slightly different from the findings of the current study. This difference may be a result of different inclusion and exclusion criteria in the study population and factors being explored that affect OC levels.

Unconditional logistic regression analysis showed that age, BMI, OC, SBP, DBP, TC, TG, PTH and FPG levels may be risk factors in the progression of hypertension in postmenopausal women. The risk of hypertension in postmenopausal women with abnormal OC levels was 8.673 times higher than that of healthy controls. In addition, the incidence of hypertension in postmenopausal women decreased with increasing OC levels. These results show that postmenopausal women with hypertension had downregulated serum OC levels.

Limitations of this study

This study still has limitations such as small sample size, single study source and incomplete inclusion factors. A prospective study with a large sample size is required in the future to analyze the specific mechanisms of the correlation of serum OC levels with hypertension.

CONCLUSION

Menopause is a risk factor for BC, and low OC levels have marked association with an elevated risk of hypertension in postmenopausal women. The findings of this study suggest that interventions aimed at increasing serum OC levels may be potential strategies for reducing the risk of hypertension in postmenopausal women. Future studies should look into the use of pharmacological agents to increase OC levels as preventative measures for hypertension in this population.

DECLARATIONS

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Ethical approval

The study was approved by the Ethics Committee of The First People's Hospital of Wenling, China (approval no. KY–2017–2012–21).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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