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Serum CTRP3 concentrations are positively correlated with disease severity in women with postmenopausal osteoporosis: a population-based cross-sectional study

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Abstract. – OBJECTIVE: Osteoporosis is a leading public health problem that contributes to increasingly high rates of osteoporotic vertebral compression fractures among older adults. This study was developed with the goal of assessing serum C1q/TNF-related protein-3 (CTRP3) levels in postmenopausal osteoporosis (PMOP) patients and exploring the correlations between these levels and PMOP severity.

PATIENTS AND METHODS: A population-based cross-sectional study of old women with osteoporosis was conducted. All women underwent both clinical and dual-energy X-ray absorptiometry examinations. Serum CTRP3, procollagen type I N propeptide (P1NP), and C-terminal telopeptide of type I collagen (CTX-1) concentrations in these patients were measured via ELISA. Bone tumor markers were additionally assessed. Receiver operating characteristic (ROC) analyses were utilized to assess the diagnostic performance of CTRP3 when identifying PMOP.

RESULTS: This study included 54 PMOP patients, 62 patients with osteopenia, and 60 age-matched patients without PMOP. Serum CTRP3 concentrations in PMOP patients were significantly lower than in the other two groups. Bone mineral density (BMD) was positively correlated with serum CTRP3 levels in all study participants, whereas it was negatively correlated with levels of P1NP and CTX-1. ROC analyses also suggested that reductions in serum CTRP3 levels may offer value as a diagnostic indicator of PMOP.

CONCLUSIONS: Present data highlight a close relationship between CTRP3 and PMOP, with lower serum CTRP3 levels being closely associated with BMD, such that they may represent a protective marker for PMOP.

Key Words:
Postmenopausal women, Osteoporosis, CTRP3, P1NP, CTX-1.

Introduction

Postmenopausal osteoporosis (PMOP) is a primary type of osteoporosis (OP) associated with estrogen deficiency, resulting in adverse outcomes that include insufficient bone formation and excessive bone resorption. PMOP patients can suffer from serious outcomes, including osteoporotic vertebral compression fractures (OVCFs), which are the most prevalent fragility fracture subtype. These fractures affect an estimated 9.7% of women with PMOP and represent an important threat to public health[1,2]. Understanding the normal processes that govern aging and patient outcomes is vital in order to aid the diagnosis and management of PMOP. The use of dual-energy X-ray absorptiometry (DXA) to measure bone mineral density (BMD) remains the gold standard approach to confirming a diagnosis of OP. While strategies that can aid in the partial treatment and prevention of PMOP are available, the pathophysiological basis for this disease remains completely understood. The early stages of OP incidence tend to be asymptomatic, and more than half of osteoporotic fractures occur in patients not meeting the BMD values necessary for the diagnosis of OP[3]. As such, more sensitive approaches to diagnosing PMOP at an earlier stage of progression are urgently needed.

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In the field of personalized medicine, studies[4,5] on biomarkers that facilitate the diagnosis and monitoring of diseases are increasingly on the rise. In recent studies[6], complement C1q tumor necrosis factor-related proteins (CTRPs) were identified as a novel subset of adipokines, exhibiting 3D structural characteristics similar to those of tumor necrosis factor (TNF) and belonging to the C1q/TNF protein superfamily[7]. In total, 15 CTRP family members with varying functions and structures have been identified to date[8]. CTRP3 is a member of this family, first identified in 2004[9], exhibiting high levels of expression in mature human and murine adipocytes, as well as high levels of expression and secretion in human mesenteric adipose tissue. In prior *in vitro* reports[10,11], CTRP3 was discovered to be involved in a range of pathological and physiological processes, regulating adipokine secretion, energy metabolism, inflammatory activity, proliferation, differentiation, and developmental processes through endocrine-like functions. Adipokines are regulatory proteins released by adipose cells that play important roles in controlling bone and cartilage homeostasis. Certain epidemiological analyses have revealed[12] that serum CTRP3 levels in obese individuals are reduced in a dependent manner on body mass index (BMI). Deng et al[13] and Ban et al[14] further observed reductions in CTRL3 concentrations in patients affected by type 2 diabetes, obesity, and hypertension as compared to healthy controls.

A growing number of studies in the literature have focused on the relationship between CTRP3 and bone metabolism. High CTRP3 expression levels have been reported[15] in adipocytes and cartilaginous tissue, and they can influence the migratory and proliferative activity of chondrocytes. Recent evidence[16] also suggests a link between this protein and diabetes, metabolic syndrome, nonalcoholic fatty liver disease, and obesity. This protein plays diverse and complex roles in the adipose tissue, liver, and bone, modulating adipokine secretion and playing a key role in the systemic regulation of bone remodeling[17]. CTRPs are also more broadly thought to serve as key adipokines that shape the interactions between endocrine and bone tissues. In one study[18], CTRP3 was identified as among the genes most highly upregulated in fracture callus tissue, and knocking out CTRP3 resulted in a delay in intrachondral fracture healing, contributing to abnormal mineral distribution, periosteal marrow compartments, and non-union. Osteoclast numbers were also reduced, and in transgenic mice overexpressing CTRP3, callus remodeling was accelerated.

While prior data from our team support a potential relationship between the regulation of CTRP3 and the pathogenesis of PMOP, the association between circulating CTRP3 levels and PMOP progression remains poorly characterized. As such, the present hospital-based case-control study was designed to assess correlations between serum CTRP3 levels and PMOP disease severity.

Patients and Methods

Subjects

Between January 2021 and September 2022, a total of 116 patients who were diagnosed with PMOP in the physical examination at the Third Hospital of Hebei Medical University were enrolled in the present analysis. The subjects were between 58 and 73 years old, and all were diagnosed with OP in accordance with World Health Organization diagnostic criteria[19]. These subjects were classified into individuals with osteopenia (n=62) and individuals with OP (n=54). In addition, 60 age- and weight-matched control women without OP were included in these analyses.

Exclusion Criteria

Participants were excluded if they: (1) had been diagnosed with any condition with the potential to confound the study results, including idiopathic or secondary OP; (2) exhibited burst fractures of the thoracic or lumbar vertebrae, pathological fractures resulting from malignancy or infection, systemic inflammatory disorders, renal diseases, or peripheral nerve or muscle diseases; or (3) had undergone any anti-OP treatments within 6 months prior to study inclusion.

This study was performed in accordance with the Helsinki Declaration and with the approval of the Ethics Committee of the Third Hospital of Hebei Medical University. All patients provided written informed consent prior to participation in this cross-sectional study.

Study Measurements

Clinical evaluation

Participant height, weight (±0.1 kg), waist and hip circumference (to the nearest 0.5 cm), and blood pressure (BP; the second of two measure-

ments with a standard mercury manometer while subjects were seated) were measured. Waist-to-hip ratio (WHR) and BMI values were calculated by the same investigator. BMI was calculated by dividing weight (kg) by height squared (m^2).

Laboratory methods

Samples of blood were collected from all subjects in the morning between 8:00 and 9:00 AM after overnight fasting. A portion of each sample was used to assess levels of total cholesterol (TC), high- and low-density lipoprotein cholesterol (LDL-C and HDL-C), fasting plasma glucose (FPG), calcium, phosphorus, alkaline phosphatase (ALP), triglycerides (TG), and measures of liver and kidney function using an autoanalyzer (Beckman CX-7 Biochemical Autoanalyzer, Brea, CA, USA).

Plasma protein analyses

Serum samples were collected by centrifuging samples (10 min, 3,000 rpm) within 30 min of collection, followed by storage at -80°C. Serum concentrations of procollagen type I N propeptide (P1NP) and C-terminal telopeptide of type I collagen (CTX-1) were measured *via* an electrochemiluminescence immunoassay approach. Serum CTRP3 concentrations were measured with an ELISA kit (Uscn Life Science Inc, Wuhan, China) based on the provided instructions. Samples were analyzed in duplicate and repeated in cases where the difference between duplicates exceeded 15%. The respective intra- and inter-assay coefficients of variance were 10% and 12%, and there was no evidence of significant interference or cross-reactivity.

Bone mineral density analyses

BMD was measured *via* DXA (MEDI LINK, Pérols, France). Lumbar vertebrae (L2-L4), right femoral neck (FN), Ward's triangle, and intertrochanter measurements were made in appropriate positions. Bone area (BA) and bone mineral content (BMC) were then used to compute BMD (g/cm^2). All measurements were performed by the same experienced investigator to minimize variations between observers. Densitometer standardization was performed before all measurements.

Statistical Analysis

Data were initially compiled in Excel 2010 and analyzed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Categorical data were compared using Chi-square tests. Normally, [non-normally] distributed continuous data were reported as means ± standard deviation [median (Interquartile range)] and compared with Student's *t*-test or one-way ANOVAs as appropriate. Correlations between BMD and serum levels of CTRP3, P1NP, and CTX-1 were performed through Pearson's correlation analyses. Receiver operating characteristic (ROC) curves were established and used to assess the value of serum CTRP3, P1NP, and CTX-1 levels when detecting PMOP. A two-sided $p<0.05$ served as the threshold to define statistical significance.

Results

Participant Characteristics

Basic patient characteristics in this study are presented in Table I. No differences among the 3 groups were observed with respect to the age of menopause, BMI, Ca, P, BUN, Scr, TG, or LDL-C levels ($p>0.05$), although the age of individuals in the OP group was higher than that of the other two groups. Serum CTRP3 levels were significantly lower in OP patients relative to other groups ($p=0.000$), while these patients exhibited higher P1NP and CTX-1 levels relative to the two other groups. BMD levels at the L2-4, femoral neck, Ward's area, greater trochanter, and intertrochanter were significantly reduced in OP patients compared to the other groups ($p<0.05$), and there was also a significant difference in these values between the control and OP groups ($p<0.05$).

Relationships Between BMD and Serum Levels of CTRP3, P1NP, and CTX-1

BMD values were positively correlated with serum levels of CTRP3 among all study participants (Table II), and BMD values were negatively correlated with bone tumor markers, indicating that CTRP3 levels may contribute to a reduction in BMD levels and bone volume.

ROC Curve Analyses

ROC curves were next employed to gauge the utility of CTRP3 as a diagnostic biomarker for PMOP. The AUC values for CTRP3, P1NP, and CTX-1 were 0.816, 0.831, and 0.765, respectively (Figure 1, Table III). This suggests that a reduction in serum CTRP3 levels may be indicative of PMOP incidence.

Table I. Study participant characteristics grouped according to osteoporosis status.

Parameter	Control group (N = 60)	Osteopenia group (N = 62)	OP group (N = 54)	*p*-value
Age (years)	59.07 ± 5.77[b]	59.29 ± 5.52[b]	61.39 ± 5.4[a]	0.054
Menopause age (years)	53 (50, 56)	54 (50.75, 56)	53 (51, 57)	0.49
Height (cm)	162.28 ± 5.19[a]	160.61 ± 5.2[a]	157.55 ± 4.83[b]	0.000
BMI (kg/m^2)	24.71 ± 2.93	24.66 ± 3.09	23.81 ± 3.15	0.218
ALP (U/L)	105.27 ± 23.23[b]	116.24 ± 32.47[b]	123.26 ± 28.22[a]	0.003
Ca (mmol/L)	2.31 ± 0.19	2.29 ± 0.19	2.25 ± 0.23	0.267
P (mmol/L)	1.11 ± 0.16	1.11 ± 0.18	1.13 ± 0.17	0.89
BUN (mmol/L)	4.67 ± 1.24	4.68 ± 1.51	4.65 ± 1.45	0.992
Scr (umol/L)	70.75 ± 24.05	71.06 ± 23.25	70.08 ± 28.63	0.978
TC (mmol/L)	5.06 ± 0.93[a]	4.65 ± 0.81[b]	4.34 ± 0.63[c]	0.000
TG (mmol/L)	1.665 (1.3425, 2.09)	1.64 (1.2825, 2.015)	1.475 (1.25, 1.885)	0.544
HDL-C (mmol/L)	1.43 ± 0.36[a]	1.33 ± 0.34[a]	1.07 ± 0.39[b]	0.000
LDL-C (mmol/L)	2.72 ± 0.57	2.68 ± 0.85	2.9 ± 0.85	0.272
CTRP3 (ng/ml)	95.02 ± 30.07[a]	79.63 ± 29.61[b]	59.56 ± 27.36[c]	0.000
P1NP (ng/ml)	34.845 (23.715, 46.72)[c]	55.24 (35.62, 69.1)[b]	62.23 (46.56, 74.0225)[a]	0.000
CTX-1 (ng/ml)	0.38 ± 0.18[b]	0.53 ± 0.21[a]	0.59 ± 0.23[a]	0.000
L2BMD (g/cm^2)	1.26 ± 0.24[a]	0.87 ± 0.33[b]	0.73 ± 0.22[c]	0.000
L3BMD (g/cm^2)	1.12 ± 0.15[a]	0.83 ± 0.25[b]	0.72 ± 0.23[c]	0.000
L4BMD (g/cm^2)	1.11 ± 0.21[a]	0.83 ± 0.21[b]	0.69 ± 0.19[c]	0.000
RNeck BMD (g/cm^2)	1.03 ± 0.19[a]	0.95 ± 0.23[b]	0.75 ± 0.23[c]	0.000
RWard BMD (g/cm^2)	0.79 ± 0.2[a]	0.65 ± 0.19[b]	0.59 ± 0.18[b]	0.000
RG.T BMD (g/cm^2)	0.79 ± 0.17[a]	0.71 ± 0.16[b]	0.61 ± 0.14[c]	0.000
RinterTro BMD (g/cm^2)	1.13 ± 0.22[a]	0.91 ± 0.16[b]	0.75 ± 0.18[c]	0.000

Different letters indicate significant differences among groups ($p < 0.05$).Data are means ± SD. OP, osteoporosis; BMI, body mass index; CA, calcium; P, phosphorus; BUN, blood urea nitrogen; Scr, serum creatinine; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CTRP3, C1q/TNF-related protein-3; P1NP, procollagen type I N propeptide; CTX-1, C-terminal telopeptide of type I collagen; BMD, bone mineral density; RG.T BMD, right greater trochanter BMD; RinterTro BMD, right intertrochanteric BMD.

Discussion

OP is the most prevalent bone metabolism disorder, resulting in characteristically high levels of bone turnover together with microstructural bone destruction, higher levels of bone fragility, and a greater risk of fracture.

In older women, bone reconstruction becomes dysregulated following menopause. While early-stage OP is generally asymptomatic prior to fracture incidence, bone turnover markers can be analyzed to gauge patient risk, guiding the diagnosis and therapeutic monitoring of PMOP. These markers include serum CTX-1 and P1NP, which

Table II. Analyses of correlations between BMD indices and CTRP3, P1NP, and CTX-1 levels.

Parameter	CTRP3 (ng/ml)		P1NP (ng/ml)		CTX-1 (ng/ml)	
	r value	*p*-value	r value	*p*-value	r value	*p*-value
L2BMD (g/cm^2)	0.243	0.001	-0.312	0	-0.289	0
L3BMD (g/cm^2)	0.294	0	-0.202	0.007	-0.308	0
L4BMD (g/cm^2)	0.286	0	-0.383	0	-0.249	0.001
RNeck BMD (g/cm^2)	0.188	0.012	-0.13	0.084	-0.102	0.179
RWard BMD (g/cm^2)	0.224	0.003	-0.207	0.006	-0.037	0.622
RG.T BMD (g/cm^2)	0.043	0.57	-0.173	0.022	-0.155	0.041
RinterTro BMD (g/cm^2)	0.352	0	-0.296	0	-0.256	0.001

BMD, bone mineral density; RG.T BMD, right greater trochanter BMD; RinterTro BMD, right intertrochanteric BMD.

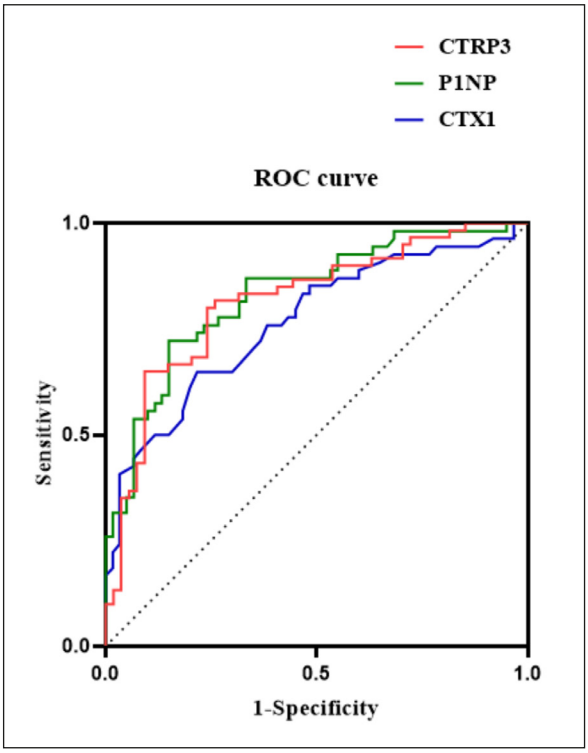

Figure 1. ROC curves for P1NP, CTX-1, and CTRP3.

are, respectively, indicators of bone resorption and formation[20]. The International Osteoporosis Foundation (IOF) currently recommends analyzing both these proteins as relevant markers of bone turnover in clinical studies[21] of OP.

This study was the first to explore PMOP patient CTRP3 P1NP, and CTX-1 levels, ultimately revealing a significant association between the concentrations of CTRP3 in the serum and BMD as a measure of PMOP severity. As such, reduced CTRP3 concentrations may be a valuable biomarker of this debilitating condition.

Here, patients with postmenopausal osteopenia exhibited increases in CTX-1 and P1NP levels, and these levels were further elevated in PMOP. These two groups also exhibited higher ALP levels compared to controls, whereas serum CTRP3 levels were lower in postmenopausal osteopenia and further reduced in PMOP patients. BMD values were also positively correlated with serum CTRP3 values, whereas they were negatively correlated with the levels of CTX-1 and P1NP among all postmenopausal participants.

At present, DXA remains the gold standard approach to assessing bone mass and volume. Here, PMOP patient BMD values for the L2-4, femoral neck, Ward's triangle, greater trochanter, and intertrochanteric areas were assessed. Serum CTRP3 concentrations were positively correlated with BMD values at all of these sites, and ROC analyses suggested that reductions in serum CTRP3 may be important for the diagnosis of PMOP. CTRP3 may also function as a predictive or protective factor for PMOP, potentially functioning as a regulator of energy metabolism and the pathology of OP through its modulation of complex interactions between adipose and bone tissue.

While adipose tissue was traditionally regarded as an important site of energy storage, it is also increasingly recognized as a major endocrine organ[22]. Adipokines are a group of hormones produced by adipocytes that may have key roles in shaping physiological and metabolic activities[23]. CTRP3 is a member of the CTRP adipokine superfamily that functions through autocrine, paracrine, and endocrine mechanisms. CTRP3 has been reported[24] to play a role in processes such as hepatic lipid metabolism and ischemic responses in cardiovascular tissue. This protein has also been shown[24] to stimulate chondrocyte, osteocyte, and chondrogenic precursor cell proliferation *via* the phosohoinositide 3-kinase (PI3K) and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways. This sug-

Table III. Evaluation of the diagnostic value of CTRP3, P1NP, and CTX-1 in postmenopausal women.

Item	AUC	SE	Sensitivity	Specificity	Youden's Index	*p*-value	95% confidence interval		Optima cut-off value
							Lower limit	Upper limit	
CTRP3	0.816	0.04	0.8	0.759	0.559	0	0.737	0.895	75.795
P1NP	0.831	0.038	0.722	0.85	0.572	0	0.756	0.906	50.76
CTX-1	0.765	0.045	0.648	0.783	0.431	0	0.677	0.853	0.525

CTRP3, C1q/TNF-related protein-3; P1NP, procollagen type I N propeptide; CTX-1, C-terminal telopeptide of type I collagen.

gests a possible role for CTRP3 in chondrocyte development and cartilage formation[25-27]. These findings suggest the possibility that CTRP3 may also play essential roles in the normal development of cartilage and bone tissue.

This report is the first to describe the value of CTRP3 as a biomarker capable of predicting PMOP incidence. However, certain limitations should be noted. First, while these results suggest a link between CTRP3 levels and PMOP, the retrospective nature of this case-control study makes it difficult to determine whether they are causally linked. Additional prospective longitudinal multicenter research will be necessary to validate the clinical relevance of CTRP3. Given the important links between obesity, OP, and related conditions, additional prospective cohort analyses focused on the roles of multiple adipokines in the regulation of OP, metabolic syndrome, fatty liver disease, and other conditions are warranted.

In summary, the present study revealed that PMOP patients exhibit significantly lower levels of serum CTRP3 compared to postmenopausal women without OP, while also highlighting a strong positive association between BMD and CTRP3 levels. CTRP3 exhibited good sensitivity and specificity when applied to identify PMOP. This report is the first to suggest that serum CTRP3 may represent a novel protective factor for PMOP. Even so, additional large-scale multicenter analyses will be necessary in the future to confirm these results and to clarify the underlying mechanisms.

Conclusions

This study found that serum CTRP3 concentrations in PMOP patients were significantly lower than in the other two groups. Bone mineral density (BMD) was positively correlated with serum CTRP3 levels in all study participants, whereas it was negatively correlated with levels of P1NP and CTX-1. ROC analyses also suggested that reductions in serum CTRP3 levels may offer value as a diagnostic indicator of PMOP. Present data highlight a close relationship between CTRP3 and PMOP, with lower serum CTRP3 levels being closely associated with BMD, such that they may represent a protective marker for PMOP.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Authors' Contribution
ZXJ contributed to the structure of the manuscript; ZD, QJ, and GJL contributed to the experiments and made the figures; ZYR and ZYZ reviewed and edited the manuscript. All authors read and approved the final manuscript.

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

Ethics Approval
This study was conducted in accordance with the ethical regulations of the Declaration of Helsinki. The experiments were approved by the Ethics Committee of the Third Hospital of Hebei Medical University. The number of Ethics Committee's acceptance is W2020-014-1.

Clinical Trial Registry
No. ChiCTR2000032134 – www.chictr.org.cn.

Informed Consent
All patients signed the informed consent form.

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