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The association between complement C1q tumour necrosis factor-related protein-1 (CTRP-1) level and metabolic syndrome

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Abstract

Introduction: Complement C1q tumour necrosis factor-related protein (CTRP-1) is a member of the C1q protein superfamily that plays a role in metabolism. This retrospective study aimed to investigate associations between CTRP-1 and metabolic syndrome (MetS).

Material and methods: This study screened subjects who had undergone regular health examinations at the Physical Examination Centre in the First People's Hospital of Yinchuan (the Second Affiliated Hospital of Ningxia Medical University) between November 2017 and September 2020. The total recruited population included 430 subjects who had undergone regular health examinations, excluding 112 subjects with high glycated haemoglobin ($HbA_{1c} \geq 7$). Finally, the data of 318 participants were further analysed. Non-diabetic subjects were divided into 2 groups: one with MetS and one without MetS (controls). Serum CTRP-1 concentrations were evaluated using an enzyme-linked immunosorbent assay.

Results: A total of 318 subjects were included, among whom 176 were diagnosed with MetS (MetS group) and 142 were not (non-MetS controls). The MetS group had significantly lower CTRP-1 levels than non-MetS controls (128.51 [111.56–143.05] *vs*. 138.82 [122.83–154.33] ng/mL, $p < 0.001$). Correlation analysis showed that serum CTRP-1 levels correlated negatively with body mass index ($r = -0.161$, $p = 0.004$), waist circumference ($r = –0.191$, $p = 0.001$), systolic blood pressure ($r = –0.198$, $p < 0.001$), diastolic blood pressure ($r = –0.145$, $p = 0.010$), fasting blood glucose (FBG) ($r = –0.562$, $p < 0.001$), fasting insulin (FIns) ($r = –0.424$, $p < 0.001$), and homeostasis model assessment of insulin resistance (HOMA-IR) ($r = –0.541$, $p < 0.001$). Multiple linear regression models showed that CTRP-1 levels were associated with MetS ($p < 0.01$). The lipid profile area under the curve (AUC) was comparable to those for FBG and FIns, and it was significantly higher than the AUCs for demographic variables.

Conclusions: The results of this study suggest that the serum CTRP-1 level is negatively associated with MetS. CTRP-1 is a potential metabolism-related protein and is likely to be associated with lipid profiles in MetS.

Key words: *CTRP-1; metabolic syndrome; triglyceride; fasting blood glucose; HOMA-IR*

Introduction

The complement C1q tumour necrosis factor-related protein (CTRPs) superfamily is a newly discovered paralogue of adiponectin, for which 15 family members (CTRP1–CTRP15) have been identified [1, 2]. Studies have shown that members of the CTRP family regulate glucose metabolism, lipid metabolism, and inflammation [3]. CTRP1 is an adipokine mainly expressed in adipose-derived cells and adipocytes. High circulating CTRP1 is associated with congestive heart disease and hypertension [4, 5]. A previous study by Lu et al. reported a decrease in atherogenesis and vascular inflammation in CTRP1-deficient apolipoprotein E knockout mice, an experiment in which atherogenesis was promoted by intraperitoneal injection of CTRP1. These data suggest that CTRP1 is associated with obesity-related metabolic and cardiovascular diseases [6]. In addition, CTRP1 levels in plasma correlate significantly with body mass index (BMI), adiponectin, and tumour necrosis factor alpha (TNF-α) in a diabetic animal mode [7].

Metabolic syndrome (MetS) is a cluster of metabolic disorders, including central obesity, insulin resistance, hypertension, and atherogenic dyslipidaemia. MetS involves multiple genetic and acquired entities under chronic low-grade inflammation and insulin resistance. If left untreated, MetS increases the risk of diabetes and cardiovascular disease (CVD) [8]. In addition to genetic and epigenetic factors, certain lifestyle and en-

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vironmental factors such as overeating and lack of physical activity have been identified as significant contributors to the development of MetS [9]. Animal studies suggest that CTRP1 may affect systemic energy metabolism under different metabolic and dietary conditions [10]. However, the relationship between MetS and CTRP1 remains unclear. Therefore, we conducted a cross-sectional, case-controlled study to investigate the associations between Mets and CTRP1 levels in subjects with MetS and healthy subjects without MetS.

Material and methods

Subjects

Subjects who underwent regular health examinations at the Physical Examination Centre in the First People's Hospital of Yinchuan (the Second Affiliated Hospital of Ningxia Medical University) between November 2017 and September 2020 were enrolled in this study. The recruited population totalled 430 persons, excluding 112 with high glycated haemoglobin ($HbA_{1c} \geq 7$). After exclusions, the data of 318 participants were further analysed. Non-diabetic subjects were divided into 2 groups: those with MetS (n = 176) and those without MetS (n = 142). According to the World Health Organization (WHO) [11], MetS is defined as meeting ≥ 3 of the following conditions: (1) waist circumference (WC): ≥ 90 cm for men and ≥ 80 cm for women; (2) systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg, under treatment, or already diagnosed with hypertension; (3) serum triglyceride ≥ 150 mg/dl; (4) high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dl for males and < 50 mg/dl for females; and (5) fasting glucose (FBG) ≥ 100 mg/dl.

Ethical considerations

The study protocol was reviewed and approved by the ethics committees of the Institutional Review Board of the First People's Hospital of Yinchuan (2020-001), and the approved guidelines were followed during the study. No informed consent was required of participants because no identifying patient information was included and the data were analysed anonymously.

Metabolic parameters data collection

The baseline demographic and clinical characteristics of each subject were recorded in the questionnaire, including age, sex, family history of type 2 diabetes mellitus (T2DM) and diabetic complications, medical history, blood pressure, height, weight, WC (cm), hip circumference (HC, cm), body mass index (BMI, kg/m^2), and waist-to-hip ratio (WHR, cm/cm).

Subjects fasted for 8 to 12 hours before 10 ml samples of peripheral venous blood were taken in ethylenediaminetetraacetic acid (EDTA) blood collection tubes. One blood sample tube was used for FBG, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), uric acid (UA), alanine transaminase (ALT), and aspartate transaminase (AST) measurement using a Beckman Coulter AU5821 automatic biochemical analyser (Beckman Coulter, Brea, CA, USA). The other tube was centrifuged, and 2 ml of serum samples were stored in −80°C refrigerators on-hold for enzyme-linked immunosorbent assay (ELISA) studies. Protein targets were studied using ELISA kits (batch number: 2017.03, Shanghai Baoman Biotechnology Co., Ltd., Shanghai, China) and a fluorescent microplate reader (Promega-GloMax, Fitchburg, WI, United States). The proteins studied were insulin, asprosin, CTRP-1, and FIns. Insulin resistance and β-cell function were evaluated using a homeostasis model. The formula for the insulin resistance index of the homeostasis model assessment (HOMA-IR) was FBG × FINS/22.5, and that for the insulin secretion index (HOMA-β) was 20 × FINS/(FBG – 3.5) [12].

Statistical analysis

The normality of continuous data was examined by the Shapiro-Wilk test. Continuous data with normal distribution were evaluated by Student's T test and are presented as mean ± standard deviation (SD); continuous data with non-normal distribution were evaluated using the Wilcoxon rank sum test and are presented as median (interquartile range; IQR); categorical data are presented as n (%) and were evaluated by the chi-square test. Spearman correlation analysis was used to assess the correlations between CTRP-1 and other covariates. To avoid collinearity, we chose one highly correlated covariate (over 0.75 of Spearman's correlation coefficient) to enter multivariate regression analysis between covariates. After using stepwise selection to enter variables with p-value < 0.20 into the model and retain variables with p-value < 0.05 through multiple linear regression analysis, the significant covariates were entered into multiple linear regression models to assess associations between CTRP-1 and variables. Multiple logistic regression was applied to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for CTRP-1 and MetS. Finally, receiver operating characteristic curves (ROCs) were plotted to assess the abilities of CTRP-1 and variables to predict MetS. Each area under the curve (AUC) was calculated, with a higher AUC indicating higher predictive performance. All P values are two-sided, and p-values of < 0.05 were considered statistically significant. All statistical analyses were performed using the statistical software package SAS software version 9.4 (SAS Institute Inc., Cary, NC, United States).

Results

The demographic and clinical characteristics of the included subjects are summarized in Table 1. Compared to controls, subjects with MetS had significantly higher BMI (median: 24.59 *vs*. 26.97 kg/m^2, p < 0.001), WC (median: 79.00 *vs*. 92.00 cm, p < 0.001), SBP (median: 122 *vs*. 137 mmHg, p < 0.001), DBP (median: 76.50 *vs*. 89.00 mmHg, p < 0.001), TG (median: 1.31 *vs*. 2.26 mmol/l, p < 0.001), LDL (median: 2.67 *vs*. 2.95 mmol/l, p < 0.001), FBG (median: 5.35 *vs* 6.12 mmol/l, p < 0.001), FINs (median: 5.30 *vs* 5.67 mmol/L, p < 0.001), and homeostasis model assessment of insulin resistance (HOMA-IR) (median: 1.22 *vs*. 1.56, p < 0.001). Additionally, compared with the controls, subjects with MetS had significantly lower HDL (median: 1.36 *vs*. 1.26 mmol/l, p < 0.001), homeostasis model assessment of insulin β (HOMA-β) (median: 54.77 *vs*. 44.68, p < 0.001), and CTRP-1 (median: 138.82 *vs*. 128.51 ng/ml, p < 0.001).

Table 2 shows the correlations between CTRP-1 levels and clinical variables in all subjects. CTRP-1 levels correlated negatively with BMI (r = –0.161, p = 0.004), WC (r = –0.191, p = 0.001), SBP (r = –0.198, p < 0.001), DBP (r = –0.145, p = 0.010), FBG (r = –0.562, p < 0.001), FIns (r = –0.424, p < 0.001), and HOMA-IR (r = –0.541, p < 0.001). CTRP-1 levels correlated positively with HOMA-β (r = 0.461, p < 0.001) (Tab. 2). After using stepwise selection, age, TG, FBG, and FIns were included

Table 1. *Associations between clinical and biochemical characteristics of metabolic syndrome (MetS) subjects and controls*

Variable	Controls (n = 142)	MetS (n = 176)	p-value
Age [years]	48 (40–53)	47 (39–52)	0.175
Sex			0.123
Male	91 (41.74)	127 (58.26)	
Female	51 (51.00)	49 (49.00)	
BMI [kg/m^2]	24.59 (21.20–25.62)	26.97 (25.24–29.08)	**< 0.001**
WC [cm]	79.00 (72.00–86.00)	92.00 (86.00–97.00)	**< 0.001**
SBP [mmHg]	122 (114–132)	137 (129–146)	**< 0.001**
DBP [mmHg]	76.50 (71.00–83.00)	89.00 (81.00–96.50)	**< 0.001**
TC [mmol/L]	5.07 (4.44–5.46)	5.05 (4.32–5.67)	0.787
TG [mmol/L]	1.31 (1.07–1.76)	2.26 (1.74–3.23)	**< 0.001**
HDL [mmol/L]	1.36 (1.23–1.51)	1.26 (1.12–1.41)	**< 0.001**
LDL [mmol/L]	2.67 (2.33–3.05)	2.95 (2.42–3.36)	**0.005**
FBG [mmol/L]	5.35 (4.86–6.02)	6.12 (5.66–6.46)	**< 0.001**
FIns [mU/L]	5.30 (4.83–5.74)	5.67 (5.23–6.06)	**< 0.001**
HOMA-IR	1.22 (1.07–1.58)	1.56 (1.31–1.70)	**< 0.001**
HOMA-β	54.77 (45.18–70.83)	44.68 (39.69–51.30)	**< 0.001**
CTRP-1 (ng/mL)	138.82 (122.83–154.33)	128.51 (111.56–143.05)	**< 0.001**

Bold P-values indicate statistical significance. MetS — metabolic syndrome; BMI — body mass index; WC — waist circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; TC — total cholesterol; TG — triglyceride, LDL — low-density lipoprotein; HDL — high-density lipoprotein; FBG — fasting blood glucose; FIns — fasting insulin; HOMA-IR — homeostasis model assessment of insulin resistance; HOMA-β — homeostasis model assessment of insulin β cell

Table 2. *Correlation of serum C1q tumour necrosis factor-related protein-1 (CTRP-1) levels with clinical variables in all subjects*

Variable	Simple		Multiple	
	r	p-value	$\beta \pm$ SE	p-value
Age	0.087	0.123	0.309 ± 0.118	**0.009**
BMI	–0.161	0.004		
WC#	–0.191	**0.001**		
SBP	–0.198	**< 0.001**		
DBP#	–0.145	**0.010**		
TC	–0.073	0.193		
TG	–0.210	0.000	–1.634 ± 0.786	**0.039**
HDL	0.069	0.223		
LDL	–0.141	0.012		
FBG	–0.562	**< 0.001**	–14.794 ± 0.786	**0.039**
FIns	–0.424	**< 0.001**	–4.708 ± 1.840	**0.011**
HOMA-IR#	–0.541	**< 0.001**		
HOMA-β#	0.461	**< 0.001**		

R — Spearman's correlation coefficient; #WC was not entered into multivariate regression analysis due to its high intercorrelation with BMI (r = 0.822; p-value < 0.001); #DBP was not entered into multivariate regression analysis due to its high intercorrelation with SBP (r = 0.806; p-value < 0.001); HOMA-IR was not entered into multivariate regression analysis due to its high intercorrelation with FIns (r = 0.91; p-value < 0.001); HOMA-IR and HOMA-β was not entered into multivariate regression analysis due to its high intercorrelation with FBG (r = 0.88; p-value < 0.001, and r = –0.89; p-value < 0.001).

Bold p-values indicate statistical significance.

BMI — body mass index; WC — waist circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; TC — total cholesterol; TG — triglyceride, LDL — low-density lipoprotein; HDL — high-density lipoprotein; FBG — fasting blood glucose; FIns — fasting insulin; HOMA-IR — homeostasis model assessment of insulin resistance; HOMA-β — homeostasis model assessment of insulin β cell

Table 3. *Associations between serum C1q tumour necrosis factor-related protein-1 (CTRP-1) and metabolic syndrome (MetS) in fully adjusted models*

Model adjustment	MetS		
	β	OR per 1 IQR* increase (95% CI)	p-value
Model 1	–0.028	0.451 (0.328–0.620)	**< 0.001**
Model 2	–0.027	0.460 (0.334–0.634)	**< 0.001**
Model 3	–0.028	0.452 (0.306–0.667)	**< 0.001**
Model 4	–0.022	0.533 (0.349–0.815)	**0.004**
Model 5	–0.016	0.633 (0.400–1.000)	0.050
Model 6	–0.002	0.932 (0.564–1.541)	0.784

Model 1 was univariate model; Model 2 — adjusted for age and sex; Model 3 — further adjusted for BMI; Model 4 — further adjusted for lipid profiles (TC, TG, LDL-C, and HDL-C); Model 5 — further adjusted for FIns.; Model 6 — further adjusted for FBG. *The IQR of CTRP-1 was 28.92.

MetS — metabolic syndrome; BMI — body mass index; TC — total cholesterol; TG — triglycerides, LDL — low-density lipoprotein cholesterol; HDL — high-density lipoprotein cholesterol; FBG — fasting blood glucose; FIns — fasting insulin

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in multivariate regression to predict the CTRP-1 level. The equation with 0.337 of adjusted R2 was:

$$Y(CTRP\text{-}1) = 233.010 - 0.309 \times Age - 1.634 \times TG - 14.794 \times FBG - 4.708 \times Fins \text{ (Tab. 2)}$$

Age increased as CTRP-1 levels increased ($\beta \pm$ SE: 0.309 ± 0.118 years, p = 0.009), while CTRP-1 levels decreased as TG, FBG, or FIns increased ($\beta \pm$ SE and p-value: –1.634 ± 0.786 mmol/l and 0.039, –14.794 ± 0.786 mmol/l and 0.039, –4.708 ± 1.840 mU/l and 0.011, respectively).

Table 3 shows the effects of CTRP-1 on MetS with increases of one interquartile range (IQR). The IQR of CTRP-1 was 28.92. In univariate analysis, the crude OR per IQR of CTRP-1 was 0.451 (95% confidence interval [CI]: 0.328–0.620). To increase model performance, we successively adjusted the variables. After adjusting for age and sex, the aOR of CTRP-1 was 0.460 (95% CI: 0.334–0.634) in model 2. The aORs of CTRP-1 were 0.452 (95% CI: 0.306–0.667) and 0.533 (95% CI: 0.349–0.815) in model 3 (further adjusted for BMI) and model 4 (further adjusted for lipid profiles [TC, TG, LDL-C, and HDL-C]). However, no significant associations were shown in model 5 (further adjusted for FIns) and model 6 (further adjusted for FBG).

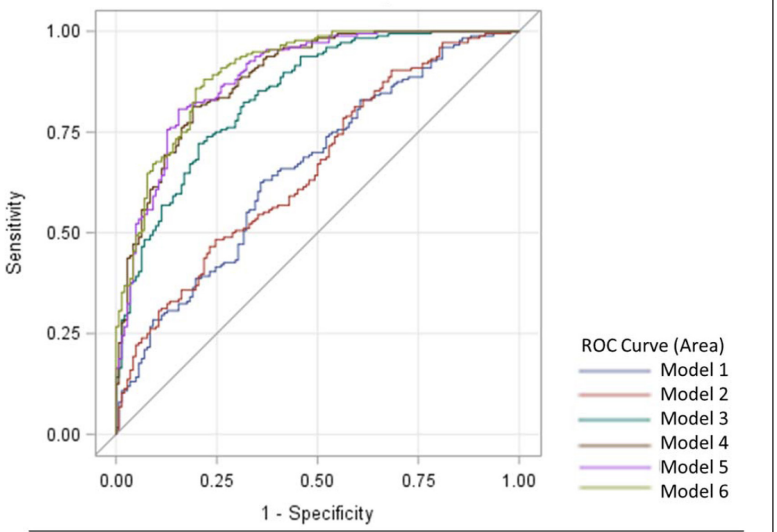
Figure 1 and Supplemental Table 1 show the areas under the curve (AUCs) for CTRP-1 for the prediction of MetS. After adjusting for age, sex, BMI, and lipid profiles (TC, TG, LDL-C, and HDL-C), the AUC of model 4 reached 0.885, which was significantly higher than that in models 1 to 3 (AUC: 0.885 *vs*. 0.658, 0.659, and 0.842, respectively). Model 6 had the best performance of AUC (0.901), with 0.881 sensitivity and 0.782 specificity. No significant differences were found in the AUCs among models 4, 5, and 6. Together these data indicated that the protein level of CTRP-1 was significantly negatively associated with lipid profiles.

Discussion

This is the first study to demonstrate that CTRP-1 levels are negatively associated with MetS. The present study separated subjects into 2 groups based on MetS status. Among all patients, the CTRP-1 levels of subjects with MetS were significantly higher than those of controls. We also found that the CTRP-1 levels correlated positively with age and negatively with TG, FBG, and FIns, suggesting that no associations are shown between CTRP-1, lipometabolism, and glycometabolism. This result indicates that the CTRP-1 level is negatively associated with MetS, suggesting that patients with MetS may have a lower level of CTRP-1 protein expression.

Results of a previous study contradicted our results because the authors demonstrated that CTRP-1 levels were significantly higher in subjects with MetS than in healthy subjects [13]. However, that study had only a small number of patients, which suggests a lack of power for achieving accurate results and may have affected statistical results. However, in the present study, 318 participants were enrolled and divided into cases and controls based on MetS status. Therefore, inclusion of more participants provided more accurate and significant statistical analysis, leading us to accept that CTRP-1 levels are negatively associated with MetS.

Nonetheless, some studies have supported our hypothesis. A previous study demonstrated that the body weight of experimental mice increased slightly in Ctrp-1 gene knockout mice compared to that in wild-type mice [10]. That study also reported that blood glucose, fasting insulin, and HAMO-IR increased significantly in the Ctrp-1 gene knockout mice. That *in vivo* study confirmed our results showing that CTRP-1 levels were negatively associated with BMI, WC, FIns, and HOMA-IR in non-diabetic patients. Therefore, sub-



	AUC (95% CI)	P-value
Model 1	0.658 (0.598, 0.718)	<0.001
Model 2	0.659 (0.599, 0.718)	<0.001
Model 3	0.842 (0.799, 0.884)	<0.001
Model 4	0.885 (0.849, 0.921)	<0.001
Model 5	0.889 (0.853, 0.925)	<0.001
Model 6	0.901 (0.868, 0.934)	<0.001

Figure 1: *Receiver operating characteristic (ROC) curve analyses. ROC curve analyses were performed for the prediction of serum C1q tumour necrosis factor-related protein-1 (CTRP-1) for metabolic syndrome (MetS)*

jects with MetS are confirmed to have a lower protein level of CTRP-1.

A previous study demonstrated that CTRP-1 levels are higher in the serum of patients with coronary artery disease and in peripheral blood mononuclear cells than in controls, and they are higher in atherosclerotic tissue than in non-atherosclerotic arterial tissue [6]. Another previous study indicated that CTRP-1 activates the S1P/cAMP signalling pathways in cardiomyocytes, suggesting that CTRP-1 plays a crucial role in the pathogenesis of ischaemic heart disease [14]. The results of these studies suggest that an increased expression level of CTRP-1 may inhibit lipometabolism and promote fat accumulation, leading to cardiovascular disease. However, the present study found that CTRP-1 was negatively associated with lipid profiles. We propose that there may be individual differences in gene profiles due to different races/ethnicities or different lifestyles and living environments, which combine to cause epigenetic change. In addition, we suggest that subjects' medication history may also change the protein expression of CTRP-1, resulting in low expression of CTRP-1 protein in subjects with MetS. Therefore, more *in vitro* and *in vivo* experiments are needed in future studies to verify our observation that low expression of CTRP-1, as found in the included subjects, may increase the risk of MetS. In addition, a recent study reported that CTRP-1 stimulated aldosterone production, and high aldosterone levels are frequently associated with obesity and MetS [15]. Therefore, increasing the protein level of CTRP1 through consumption of nutritious protein-rich foods or certain medications is a potential therapeutic target for patients with MetS.

The present study has several limitations. First, it is a retrospective study, which limits the extent of generalizing results to other populations and may include unavoidable selection bias in statistical analyses. Second, further *in vitro* experiments are still needed to clarify the mechanism underlying associations between CTRP-1 and lipometabolism.

Conclusion

The results of this study demonstrate that the CTRP-1 level is negatively associated with MetS. CTRP-1 is negatively associated with lipid profiles, suggesting that subjects with lipometabolism disorder may tend to have lower protein expression of CTRP-1. These

results may provide useful information for physicians to screen subjects at high-risk for MetS.

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Conflict of interest
The authors declare that there is no conflict of interest

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