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Decreased serum C1Q/TNF-related protein 4 concentrations are associated with type 2 diabetes mellitus

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Abstract

Objective: To detect serum C1Q/TNF-related protein 4 (CTRP4) concentrations in patients with newly diagnosed type 2 diabetes mellitus (T2DM) and evaluate the correlation between CTRP4 and other variables in T2DM.

Method: Sixty-five patients with newly diagnosed T2DM and eighty-nine healthy volunteers were enrolled in this study. Anthropometric and biochemical data of the study participants was collected, and serum CTRP4 concentrations were detected by enzyme-linked immunosorbent assay (ELISA) kit. The correlation between serum CTRP4 and other indexes was analyzed by Spearman correlation analysis. Trend χ^2 test and binary multivariate stepwise logistic regression were performed to assess the correlation between CTRP4 and the risk of T2DM.

Results: Serum CTRP4 concentrations in the T2DM group were significantly lower than those in the control group ($P < .01$). Spearman correlation analysis showed that CTRP4 concentrations were negatively correlated with BMI, hs-CRP, HOMA-IR, FBG and TG ($r =$ - 0.430, - 0.453, - 0.371, - 0.361, - 0.506, $P < .05$), and positively correlated with HDL-c ($r = 0.303$, $P < .05$). Trend χ^2 test indicated that with the increase of CTRP4 levels in the population, the risk of T2DM presented a general downward trend ($P < .01$). Binary multivariate stepwise logistic regression suggested that serum CTRP4 was an independent impact factor for T2DM and high serum CTRP4 levels were related to the decreased risk of T2DM ($P < .05$).

Conclusions: Serum CTRP4 concentrations decrease in patients with newly diagnosed T2DM. Serum CTRP4 levels are negatively associated with the risk of T2DM.

Keywords: cross-sectional study, CTRP4, type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) has been a global threat to people's health, affecting more than 450 million people and accounting for more than 760 billion dollars financial expenditure worldwide.[1] It is also a potential trigger factor of many other diseases, such as cardiovascular disease, cerebrovascular disease[2,3] and renal disease.[4] T2DM has been regarded as one of the main factors that seriously reduce human's life expectancy.[5]

C1Q/TNF-related protein (CTRP) is a homologous superfamily of adiponectin.[6] Previous studies have found that CTRP superfamily has many physiological functions, including regulating inflammatory process, glycolipid metabolism, and the function of vascular endothelium.[7–9] C1Q/TNF-related protein 4 (CTRP4), belonging to CTRP superfamily, is a new member of adipocytokine. It is widely expressed in adipose tissue, brain, bone marrow stem cells and circulatory system.[10] CTRP4 is a vital regulator of inflammation. It is closely involved in inflammatory response[11] and regulates inflammatory signaling pathways during tumorigenesis.[12,13] Besides, CTRP4 was reported to function on the hypothalamus to modulate food intake and energy homeostasis.[14–16] T2DM, as a chronic inflammation-associated metabolic disease, is also closely

related to food intake behaviors[17,18] and energy homeostasis. However, little is known about the association between CTRP4 and T2DM. Therefore, to elucidate the relationship between CTRP4 and T2DM, we detected the concentrations of serum CTRP4 in patients with newly diagnosed T2DM and analyzed the relationship between CTRP4 and T2DM.

Participants and methods

Participants

A total of 65 patients with newly diagnosed T2DM were enrolled consecutively at the First Affiliated Hospital of Soochow University from October 2020 to April 2021. All patients met the 2019 American Diabetes Association (ADA) diagnostic criteria for diabetes. They did not receive any treatment for T2DM, including medication, diet control, exercise interventions, or blood glucose monitoring. The exclusion criteria included: (1) type 1 diabetes or other types of diabetes; (2) age below 18 years old or above 70 years old; (3) acute infection or in acute stress state;(4) hypertension, cardiovascular disease, severe liver, kidney or other systemic diseases; (5) have received hypoglycemic drug therapy or have taken other drugs which may impact on metabolism; and (6) malignant tumors.

Eighty-nine healthy volunteers were enrolled from the medical center of the First Affiliated Hospital of Soochow University. The healthy volunteers were screened to match the patients of the case group in sex, age and body mass index (BMI) and were given a 75 g oral glucose tolerance test (OGTT) to make sure that they were normal in glucose regulation, that is, fasting blood glucose $<$ 6.1 mmol/L and 2 h post-OGTT blood glucose $<$ 7.8 mmol/L.

Our study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 2021110). All the individuals enrolled in our study provided written informed consent.

Anthropometric and biochemical data collection

Anthropometric measurements, including height and weight, were collected by professionals. BMI was calculated as body weight (kg) divided by height (m) squared. All participants were fasting for 10 h, and 5 mL venous blood was collected the next morning. Fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL-c), high density lipoprotein (HDL-c), creatinine (Cr), alanine aminotransferase (ALT), uric acid (UA) and high sensitive C-reactive protein (hs-CRP) were measured by a Hitachi 7600 automatic biochemical analyzer. HbA1c was determined by a high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA). Fasting insulin (FIN) was assessed by an automated immunoassay analyzer (AIA-2000ST, TOSOH company, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as FIN (μU/mL) times FBG (mmol/L) divided by 22.5. The concentrations of serum CTRP4 from the plasma were detected by ELISA kit (Raybiotech, UAS). The sensitivity of CTRP4 ELISA kit is 0.78 ng/mL, intra-assay precision and inter- assay precision are 4%–6% and 8%–12%, respectively.

Statistical analysis

SPSS 23.0 (IBM, USA) was performed to analyze data. The normal distribution of continuous variables was determined by Shapiro-Wilk test. Variables normally distributed are presented as mean ± standard deviation, while variables non-normally distributed were presented as median (interquartile range). For variables non-normally distributed, a natural logarithmic transformation was performed before further analysis. Continues variables with normally distribution and variables presented normally distribution after logarithmic transformed were compared by two independent sample t-test. Data with non-normally distribution were compared by Mann–Whitney U test. Categorical data were detected by χ^2 test. The correlation between CTRP4 and other clinical variables was analyzed by Spearman correlation analysis. To assess the independent impact factors of T2DM, binary multivariate stepwise logistic regression was conducted. To investigate the association between CTRP4 and the risk of T2DM, the participants were divided into 4 groups according to the quartiles of CTRP4, that is: quartile 1: $<$6.21 ng/mL; quartile 2: 6.21–10.53 ng/mL; quartile 3: 10.54–15.28 ng/mL; quartile 4: $\geqslant$ 15.29 ng/mL. Then trend χ^2 test and binary multivariate stepwise logistic regression were performed. Before logistic regression analysis, variance inflation factor (VIF) was adopted to screen the multicollinear variables.

Variables with VIF >10 was considered to be collinear and were screened out the logistic regression model. $P<.05$ indicated a statistically significant difference.

Results

Clinical characteristics and biochemical indicators of the participants

The clinical characteristics and biochemical indicators of the 65 newly diagnosed T2DM patients and 89 healthy volunteers were showed in Table 1. No statistically differences were found in gender, age, BMI, TC, LDL-c, Cr and ALT between the two groups. CTRP4 concentrations in the T2DM group were significantly lower than those in the control group (9.43 (7.57) vs 11.89 (14.30) ng/mL, $P<.01$). Besides, patients in the T2DM group had higher HbA1c, TG, FBG, FIN, HOMA-IR, UA and hs-CRP, while lower HDL-c compared to the participants in the control group ($P<.05$).

Correlation between CTRP4 and other variables

According to Spearman correlation analysis, CTRP4 levels were negatively correlated with BMI ($r = -0.361$, $P=.003$), hs-CRP ($r=-0.430$, $P=.028$), HOMA-IR ($r=-0.453$, $P<.001$), FBG ($r=-0.371$, $P=.002$) and TG ($r=-0.506$, $P<.001$), and positively correlated with HDL-c ($r=0.303$, $P=.014$) (Figure 1). However, CTRP4 levels were not associated with HbA1c, FIN, TC, LDL-c, and other variables (Table 2).

The association between CTRP4 and T2DM

From the quartile 1 to the quartile 4 of CTRP4, the percentage of T2DM was 69.23%, 34.21%, 43.59% and 21.05%, respectively. The result indicated that with the increase of CTRP4 levels in the population, the percentage of T2DM presented a general downward trend. The trend χ^2 test showed that the difference was statistically significant ($P<.01$).

To assess the impact factors of T2DM, binary multivariate stepwise logistic regression was performed. T2DM was taken as the dependent variable, and the variables with $P<.05$ in the binary univariate logistic regression were taken as the alternative independent variables. After screening the multicollinear variables with VIF >10, age, LDL-c, UA, TG, HDL-c, hs-CRP and CTRP4 were selected into the regression model as independent variables. According to the binary multivariate stepwise logistic regression analysis, HDL-c and serum CTRP4 were independent impact factors for T2DM (Table 3).

Table 1. Clinical characteristics and biochemical indicators of the study objects.

Variables	T2DM	Control group	*P* value
Sex (M/F)	32/33	43/46	.881
Age[a] (years)	51.17 ± 15.03	50.60 ± 6.79	.775
BMI[a] (kg/m^2)	22.37 ± 1.58	21.98 ± 1.58	.135
HbA1c[a] (%)	12.07 ± 1.74	5.62 ± 0.29	<.001△
TC[a] (mmol/L)	4.92 ± 0.89	4.97 ± 0.89	.731
TG[b] (mmol/L)	1.34 (1.15)	1.03 (0.8)	<.001△
HDL-c[c] (mmol/L)	0.96 (0.26)	1.44 (0.45)	<.001△
LDL-c[a] (mmol/L)	3.05 ± 0.86	2.78 ± 0.80	.053
Cr[c] (μmol/L)	55.9 (11.55)	54 (17.7)	.522
ALT[c] (U/L)	19.70 (15.15)	20.8 (20.65)	.206
FBG[b] (mmol/L)	8.75 (4.53)	4.89 (0.63)	<.001△
FIN[a] (μU/mL)	10.54 ± 4.22	5.53 ± 2.26	<.001△
HOMA-IR[a]	4.35 ± 2.16	1.22 ± 0.56	<.001△
UA[b] (μU/mL)	320.9 (123.3)	277.6 (78.35)	<.001△
hs-CRP[c] (pg/mL)	1.58 (2.42)	1.05 (1.57)	.045△
CTRP4[c] (ng/mL)	9.43 (7.57)	11.89 (14.30)	<.001△

ALT, alanine aminotransferase; BMI, body mass index; Cr, creatinine; CTRP4, C1Q/TNF-related protein 4; F, female; FBG, fasting blood glucose; FIN, fasting insulin; HDL-c, high density lipoprotein; HOMA-IR, Homeostasis model assessment of insulin resistance; hs-CRP, high sensitive C-reactive protein; LDL-c, low density lipoprotein; M, male; TC, total cholesterol; T2DM, type 2 diabetes mellitus; TG, triglyceride; UA, uric acid.
Continues variables with normally distribution are presented as mean ± standard deviation. Variables non-normally distributed were presented as median (interquartile range). Sex of the two groups was compared by χ^2 test.
[a]Continues variables with normally distribution.
[b]Variables presented normally distribution after logarithmic transformed were compared by two independent sample t-test.
[c]Data with non-normally distribution were compared by Mann–Whitney U test.
△Statistically significant difference with $P<.05$.

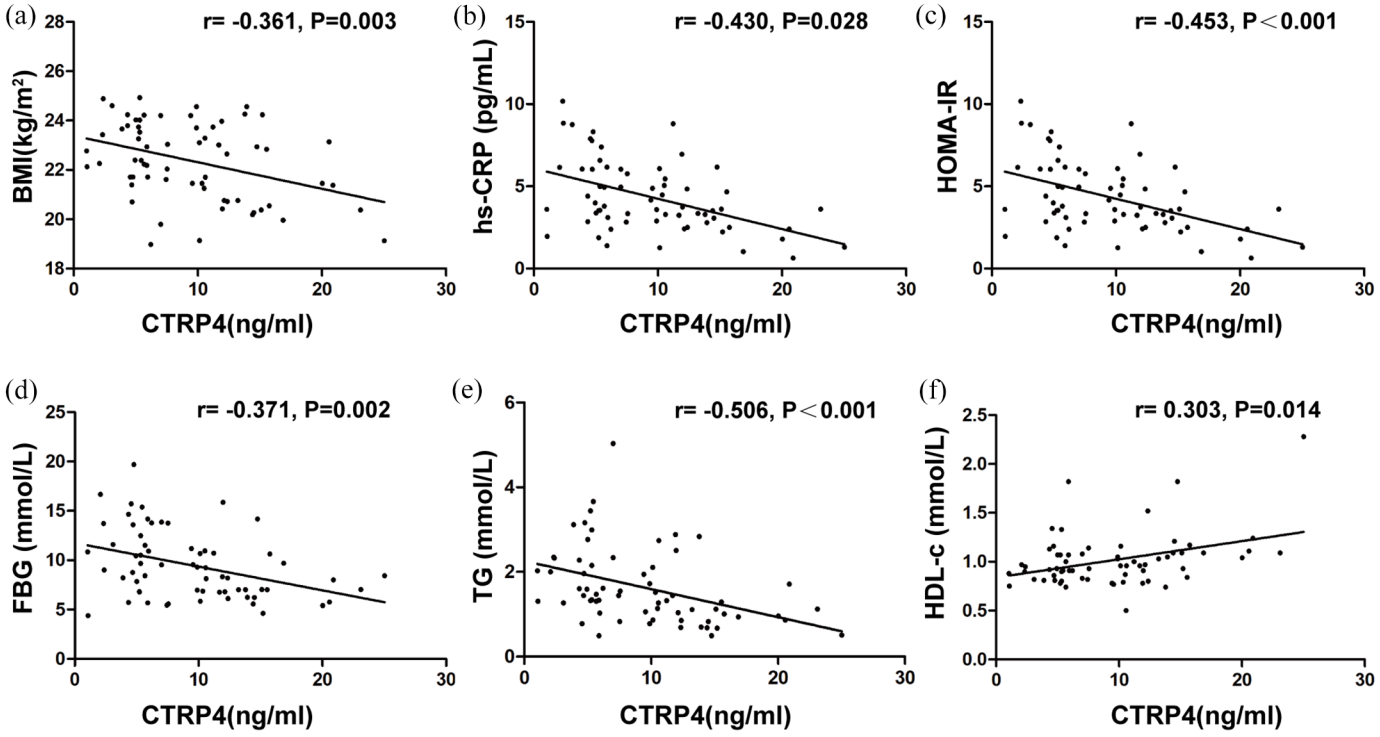

Figure 1. Scatter plots showing the correlation between CTRP4 concentrations and (a) BMI, (b) hs-CRP, (c) HOMA-IR, (d) FBG, (e) TG and (f) HDL-c in T2DM patients.

Taken CTRP4 as classification variable (quartile 1–4) for the regression model, the binary multivariate stepwise logistic regression analysis showed that when the top quartile of CTRP4 compared with the bottom, an OR of 21.8% (95% CI: 0.060–0.792, $P<.05$) was observed (Table 4).

Discussion

Soluble factors are involved in T1DM/T2DM pathogenesis[19,20] and the onset of many long-term diabetic complications.[21,22] CTRP superfamily is a group of secreted soluble proteins, many members of which were found to be related to T2DM and its complications. CTRP3 and CTRP9, for

Table 2. Spearman correlation analysis of CTRP4 and other clinical parameters.

	BMI△	HbA1c	FIN	ALT	Cr	hs-CRP△	HOMA-IR△
r	−0.361	0.014	−0.166	−0.196	0.117	−0.430	−0.453
P	0.003	0.913	0.187	0.117	0.354	0.028	<0.001
	FBG△	**UA**	**TC**	**TG△**	**HDL-c△**	**LDL-c**	
r	−0.371	−0.025	−0.103	−0.506	0.303	−0.081	
P	0.002	0.84	0.416	<0.001	0.014	0.523	

ALT, alanine aminotransferase; BMI, body mass index; CTRP4, C1Q/TNF-related protein 4; FBG, fasting blood glucose; FIN, fasting insulin; HDL-c, high density lipoprotein; HOMA-IR, Homeostasis model assessment of insulin resistance; hs-CRP, high sensitive C-reactive protein; LDL-c, low density lipoprotein; TC, total cholesterol; TG, triglyceride; UA, uric acid.
△Statistically significant difference with $P<.05$.

example, has recently been thoroughly studied and were reported to play a protective role in T2DM and diabetic complications.[9,23] CTRP4 is a novel member of CTRP superfamily, but unlike the other members in the superfamily with a single C1q globular domain, it is unique in possessing two tandem C1q domains connected by a short linker.[16] CTRP4 has been shown to act in the hypothalamus through activating STAT3 signaling pathway to suppress food intake.[15] CTRP4 deficiency mice showed increased serum cholesterol levels and impaired glucose tolerance.[14] However, little is known regarding the role of CTRP4 in T2DM. To the best of our knowledge, this is the first study elucidating the association between serum CTRP4 and T2DM. Since our study was cross-sectional, the causal relationship between serum CTRP4 and T2DM couldn't be confirmed, the conclusion from the study should be interpreted with caution.

In this study, for the first time we found that the serum CTRP4 levels in newly diagnosed T2DM were significantly decreased compared with the healthy controls. The differential expression profile of serum CTRP4 in T2DM gave evidence that CTRP4 might have a close relationship with T2DM. Byerly *et al.*[16] reported that CTRP4 showed a modulating role in energy metabolism. Sarver *et al.*[14] reported that loss of CTRP4 induced elevated serum cholesterol levels and impaired glucose tolerance in male mice. Consistent with their reports, we also found clues about the potential role of CTRP4 in regulating glycolipid metabolism and insulin resistance: our study showed that CTRP4 was negatively correlated with FBG, TG, BMI and HOMA-IR in T2DM patients. However, to further elucidate the role of CTRP4 and the potential mechanism in glycolipid metabolism, more studies need to be conducted.

Chronic low-grade inflammation is regarded as one of the most important factors in the initiation and pathogenesis of T2DM. Increased numbers of inflammatory cells are infiltrated in adipose tissue, which produces proinflammatory cytokines and leads to insulin resistance and glucose metabolic disorder.[24] CTRP4 is closely associated with inflammation in many physiological processes but its role has not been fully identified. It was reported that CTRP4 was involved in the modulation of innate immunity through acting with nucleolin.[25] CTRP4 could significantly inhibit the activation of caspase-1/IL-1β inflammatory pathway in model rats with preeclampsia.[26] It also showed an anti-inflammatory property in macrophages[11] and could suppress the NF-κB signaling pathway to ameliorate leptin resistance in mice with diet-induced obesity.[27] However, there are conflicting reports regarding the role of CTRP4 in cancer-related inflammation. Luo *et al.*[12] found CTRP4 could relieve the colitis symptom and suppress the colitis-associated colorectal cancer in mice. Controversially, Li *et al.*[13] reported CTRP4 could activate STAT3 and NF-κB inflammatory pathways in human cancer cells. In our study, we observed a significant correlation between CTRP4 and hs-CRP, which implying that CTRP4 might be involved in the chronic low-grade inflammation of T2DM. However, many other proinflammatory cytokines are also associated with the chronic low-grade inflammation of T2DM, such as tumor necrosis factor α (TNF-α), monocyte chemotactic protein 1 (MCP-1) and interleukins 6 (IL-6).[28] To further assess the correlation between CTRP4 and chronic low-grade inflammation of T2DM, more proinflammatory cytokines need to be detected.

Table 3. Binary multivariate stepwise logistic regression of the independent factors for T2DM (CTRP4 as continuous variable).

Variables	β	SE	Wald	P value	Exp(B)	95%CI
HDL-c	−5.771	1.016	32.277	<0.001	0.003	0.000–0.023
CTRP4	−0.060	0.029	4.401	0.036	0.942	0.890–0.996

CI, confidence interval; CTRP4, C1Q/TNF-related protein 4; HDL-c, high density lipoprotein; SE, standard error; T2DM, type 2 diabetes mellitus.

Table 4. Binary multivariate stepwise logistic regression of the independent factors for T2DM (with quartiles of CTRP4).

Variables	β	SE	Wald	*P* value	Exp(B)	95%CI
HDL-c	−6.211	1.110	31.316	<.001	0.002	0.000–0.018
CTRP4[a]						
quartile 2	−1.561	0.669	5.454	.020	0.210	0.057–0.778
quartile 3	−1.255	0.639	3.851	.050	0.285	0.081–0.998
quartile 4	−1.523	0.658	5.356	<.001	0.218	0.060–0.792

CI, confidence interval; CTRP4, C1Q/TNF-related protein 4; HDL-c, high density lipoprotein; SE, standard error; T2DM, type 2 diabetes mellitus.
[a]Quartile 1 of CTRP4 was taken as reference in the binary logistic regression analysis.

In our study, we found that CTRP4 was an independent impact factor for T2DM, and the risk of T2DM gradually decreased across increasing quartiles of CTRP4. Compared to quartile 1 of CTRP4, the ORs of the other 3 quartiles were all around 20%. We noted the *P* value was just equal to 0.050 for the OR of the quartile 3 of CTRP4. The reason for this result might be that our sample size was relatively small. Larger samples are required in the future, and the result may be significant as the sample size increases.

There are still several limitations in our present study. First, our research is a single center hospital-based study, the number of the samples is relatively small, multiple centers and larger samples are required in the future. Second, as a cross-sectional study, it is not possible to explain causal relationship between CTRP4 and the development of T2DM. Cohort studies and basal experiments at the animal and cellular levels are necessary to investigate the role of CTRP4 in the development of T2DM.

In conclusion, for the first time, we observed that serum CTRP4 concentrations were decreased in people with T2DM. In addition, CTRP4 levels were negatively correlated with BMI, hs-CRP, HOMA-IR, FBG, TG, and positively correlated with HDL-c. Serum CTRP4 was an independent impact factor for T2DM and the levels of serum CTRP4 were negatively associated with the risk of T2DM. Our study is cross-sectional, and was performed in a single center with a relatively small sample size. Given these limiations, and as there are few studies on the correlation between CTRP4 and T2DM, the role of CTRP4 in T2DM and its mechanism need to be further explored.

Author contributions

Liu, Zheng: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Writing-original draft.

Lu, Jinhua: Data curation; Investigation; Methodology.

Zhang, Daiyi: Data curation; Investigation; Methodology.

Niu, Lijuan: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Writing-review & editing.

Shi, Bimin: Project administration; Supervision; Writing-review & editing.

Conflict of interest statement

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