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CLINICAL TRIAL

Circulating complement-1q tumor necrosis factor-α-related protein isoform 5 levels are low in type 2 diabetes patients and reduced by dapagliflozin

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Complement-1q tumor necrosis factor-α-related protein isoform 5, Sodium–glucose cotransporter 2 inhibitor, Type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: As a member of the tumor necrosis factor-α-related protein family, complement-1q tumor necrosis factor-α-related protein isoform 5 (CTRP5) has been found to be associated with obesity and insulin resistance (IR). Previous studies in humans and animals have reported contradictory results related to the association between CTRP5 and IR. The purpose of the present study was to explore the relationship between CTRP5 and IR through a cross-sectional study and drug intervention study of type 2 diabetes patients.

Materials and Methods: A cross-sectional study was carried out with 118 newly diagnosed patients with type 2 diabetes and 116 healthy adults. In an interventional study, 78 individuals with newly diagnosed type 2 diabetes received sodium–glucose cotransporter 2 inhibitor (dapagliflozin) treatment for 3 months. Circulating CTRP5 concentrations were measured by enzyme-linked immunosorbent assay.

Results: Serum CTRP5 concentrations were markedly reduced in patients with type 2 diabetes when compared with those of healthy individuals ($P < 0.01$). When considering the study population as a whole, individuals with IR (homeostasis model of assessment of IR ≥2.78) had lower CTRP5 concentrations than the individuals without IR (homeostasis model of assessment of IR <2.78; $P < 0.01$). Serum CTRP5 negatively correlated with age, body mass index, waist-to-hip ratio, Systolic blood pressure, triglyceride, total cholesterol, glycated hemoglobin, fasting blood glucose, 2-h blood glucose, fasting insulin and homeostasis model of assessment of IR. After 12 weeks of sodium–glucose cotransporter 2 inhibitor treatment, serum CTRP5 levels in type 2 diabetes patients were significantly reduced accompanied with ameliorated glycometabolism and IR compared with before treatment ($P < 0.01$).

Conclusions: CTRP5 is likely a marker for type 2 diabetes in humans.

INTRODUCTION

The complement-1q tumor necrosis factor-α (TNF-α)-related protein family (CTRPs) includes 15 members that have similar structure and function to adiponectin (Adipoq)[1]. CTRPs are widely expressed in various tissues in animals and humans, and have important metabolic functions[2–8]. Because Adipoq is relative to energy homeostasis and insulin sensitivity *in vivo*, it is important to investigate the physiological function of each member of the CTRPs family and the changes in circulating levels in an insulin-resistant state. Previous studies have shown that members of the CTRPs family[5,8–10] might be related to

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energy equilibrium and insulin resistance (IR). In addition, in individuals with obesity, metabolic syndrome and type 2 diabetes, plasma levels of some CTRPs, such as CTRP9, CTRP1and CTRP3, were found to increase or decrease[11–14]. In mice, CTRP1, CTRP3 and CTRP9 have been found to be related to the onset of IR, obesity and hepatic steatosis[3,7].

CTRP5 is a 25 kDa secretory glycoprotein encoded by C1QTNF5. This cytokine is mainly expressed in adipose tissue, skeletal muscle, basal lamina, retinal epithelium and so on[15–17]. The CTRP5 deoxyribonucleic acid sequence is highly conserved and has three conserved domains: a signal peptide, a collagen and C1q domain[17]. Ten years ago, a genome-wide association study reported that a polymorphism of CTRP5 gene was associated with the development of metabolic syndrome in a Japanese patient[18]. An increasing CTRP5 expression was found in subcutaneous fat in obese individuals using microarray analysis[16]. Park *et al.* found that serum CTRP5 levels were increased in IR-related rat and mice, such as *db*/*db* mice and OLETF rats[15]. Furthermore, CTRP5 increased glucose uptake by increasing the activity of AMPK and promoted the translocation of glucose transporter-4 in the cell membrane. In the *in vitro* study, CTRP5 was also found to increase the phosphorylation of acetyl coenzyme A carboxylase and stimulate the oxidation of fatty acids[15]. In the other study, CTRP5 treatment led to the inhibition of Adipoq release and secretion in fat cells[19].

In recent years, it has been reported that insulin-induced Akt phosphorylation (a key component of insulin signals) in fat and muscle tissues is inhibited by the treatment of CTRP5 protein[20]. Based on these findings, CTRP5, as a new secreted protein, might be involved in the incidence of IR and type 2 diabetes. However, data are lacking on the correlation between CTRP5 and type 2 diabetes in humans.

Sodium–glucose cotransporter 2 inhibitor (SGLT2i) is a newly discovered hypoglycemic drug. Recently, SGLT2i has been found to reduce weight gain by a high-fat diet, increase lipolysis and fat browning, elevate the circulating levels of cytokines, such as fibroblast growth factor 21, and improve IR *in vivo*[21].

In the current study, we hypothesized that IR could alter circulating levels of CTRP5, and circulating CTRP5 might be regulated by dapagliflozin, a SGLT2i. Therefore, the objectives of the present study study were as follows: (i) to determine circulating levels of CTRP5 in newly diagnosed type 2 diabetes patients and healthy participants; (ii) to investigate the relationship between circulating CTRP5 and IR; (iii) to observe the effect of SGLT2i treatment on circulating CTRP5 in type 2 diabetes patients.

METHODS

Study population

A total of 234 Chinese Han individuals participated in the current study, including 118 newly diagnosed type 2 diabetes patients and 116 healthy individuals, 78 type 2 diabetes patients received SGLT2i treatment, a detailed flow diagram is shown in Figure S1. The diagnosis of type 2 diabetes was based on a 75-g oral glucose tolerance test according to the diagnostic criteria from the American Diabetes Association[22]. All patients were not treated with any antidiabetic agents, insulin, diet control or physical exercise. Type 1 diabetes patients and type 2 diabetes patients with acute and chronic complications, hypertension, liver cirrhosis, hepatic and renal failure, congestive heart failure or other major diseases were excluded from this study. Age- and sex-matched healthy individuals without any clinical evidence of diseases (body mass index [BMI] ranged 18–24 kg/m^2) were recruited from the community or schools through advertisement or routine medical checkup, and were used as the controls. The oral glucose tolerance test was carried out for the control individuals to exclude type 2 diabetes and impaired glucose tolerance, and individuals with a family history of type 2 diabetes were also excluded. None of these individuals used any medications that alter glucose and lipid metabolism. All individuals who participated the present study were asked to sign informed consent before the start of the experiment. This study was approved by the ethics committee of Chongqing Medical University in accordance with the World Medical Association Declaration of Helsinki[23].

Measurements of anthropometric, biochemical and cytokine parameters

Bodyweight (kilograms) / height squared was used to calculate BMI. The waist-to-hip ratio (WHR) was calculated by the measurements of waist and hip circumferences. The percentage of fat *in vivo* was measured by bioelectrical impedance (BIA-101; RJL Systems, Shenzhen, China). The equation used to calculate homeostasis model assessment of IR (HOMA-IR) was fasting insulin (mU/L) × fasting blood glucose (FBG; mmol/L) / 22.5[24]. The 75th percentile value of HOMA-IR from the healthy individuals was selected as the cut-off point to define IR[25]. Therefore, the IR was defined as HOMA-IR ≥2.78. After a 10-h overnight fast, blood samples were collected, and glucose and glycated hemoglobin (HbA1c) were immediately measured by the glucose-oxidase method and anion-exchange high-performance liquid chromatography. Serum was separated and was stored at –80°C for the measurement of biochemical and cytokine parameters.

Human CTRP5 (Cat. #) enzyme-linked immunosorbent assay kit was purchased from Aviscera Bioscience Inc. (CA, USA) with the following measurement index: intra- and interassay coefficients of variance were 6–8% and 8–12%, respectively. Linearity was in the range of 1.56–100 μg/L. The limit of detection for this assay was 0.5 μg/L. Insulin was measured with chemiluminescence. Blood fat, free fatty acids, alanine transaminase, aspartate transaminase and serum creatinine were measured with commercial kits (Roche, Shanghai, China), as previously described[26].

Interventional study

A total of 78 patients with type 2 diabetes, including 38 women and 40 men, attended this self-controlled clinical study of

SGLT2i treatment without a placebo-controlled group. The inclusion criteria included age 40–70 years; BMI of 25–35 kg/m^2, and HbA1c levels between 6.5 and 9.0%. Patients with type 1 diabetes, ketoacidosis, a history of hypoglycemia unawareness, malignant disease or any other diseases were excluded. These patients were treated with dapaglifozin (AstraZeneca, Jiangsu, China) 10 mg once daily before breakfast for 12 weeks. All patients were asked to maintain their former lifestyle and dietary habits during the study. Patients with three FBG readings >14 mmol/L were withdrawn from the study to prevent acute complications. Blood samples were collected at 08.00 h on day 1 before treatment and on day 2 of the last treatment for the measurements of biochemical parameters and CTRP5. The study was approved by the ethics committee of Chongqing Medical University. All participants provided written informed consent.

Statistical analysis

The sample size is calculated as follows. $N = [Z_{\alpha/2}\sigma/\varepsilon\mu]^2$ (σ, standard; μ, mean; $Z_{\alpha/2} = 1.96$, $\alpha = 0.05$, $\varepsilon = 4\%$). The normal distribution of variables was evaluated by the Kolmogorov–Smirnov test. Data are the mean ± standard deviation or median (interquartile range). Differences between groups were assessed by ANOVA, an unpaired *t*-test or a paired *t*-test. Spearman's correlation analysis was used to examine the association of CTRP5 levels with other parameters. Multiple stepwise regression analysis was used to investigate the relationship between CTRP5 and the other variables, with CTRP5 as a dependent variable. Multivariate logistic regression analysis was used to investigate the association of CTRP5 with type 2 diabetes. Row mean scores and Cochran–Armitage trend test of the impact of plasma CTRP5 level on type 2 diabetes were carried out. Receiver operating characteristic (ROC) curve analyses were used to evaluate the performance of CTRP5 in the diagnosis of type 2 diabetes by calculating the area under ROC curve (AUC). The maximum sensitivity and specificity of CTRP5 to predict type 2 diabetes were determined by the Youden Index. The comparison of the AUC was carried out by a $P < 0.05$. The greater AUC represents the higher diagnostic value for CTRP5 to differentiate the diseases. All data were based on two-sided tests. All analyses were carried out by statistical software SAS version 22.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Main clinical features and CTRP5 levels in study populations

The anthropometric, biochemical and cytokine parameters in study participants are shown in Table 1. Type 2 diabetes patients had higher BMI, WHR, systolic blood pressure, FBG, 2-h blood glucose after glucose overload (2 h-BG), HOMA-IR, HbA1c, triglyceride and total cholesterol than controls ($P < 0.01$ or 0.05). In the current study, fasting CTRP5 concentrations were measured in 116 healthy adults (aged 40–70 years). Figure S2a shows the distribution of circulating CTRP5 concentrations in these participants. In healthy participants, the range of CTRP5 concentration was 85.11–235.16 μg/L. Circulating levels of CTRP5 were between 90.74–228.21 μg/L for 95% healthy participants. Importantly, circulating levels of CTRP5 were markedly lower in type 2 diabetes patients than in the controls ($P < 0.01$; Figure 1a), and the reduction of CTRP5 in type 2 diabetes patients remained significant after age, sex and BMI adjustment ($P < 0.01$; Table 1). However, there was no difference in serum CTRP5 levels between men and women (118.05 ± 34.87 vs 125.82 ± 35.05 μg/L). In addition, circulating levels of CTRP5 were also no different between overweight/obese (BMI ≥25 kg/m^2) and lean individuals (BMI <25 kg/m^2; 118.51 ± 38.36 vs 125.13 ± 33.35 μg/L). Intriguingly, individuals with IR (HOMA-IR ≥2.78) had lower CTRP5 concentrations than individuals without IR (HOMA-IR <2.78; (110.88 ± 31.97 vs 140.07 ± 32.25 μg/L, $P < 0.01$; Figure S2b).

Correlation of CTRP5 with clinical and biochemical parameters

Next, we analyzed the association of CTRP5 with other parameters in the entire study population. We found that the CTRP5 concentrations of circulation correlated negatively with age, BMI, WHR, systolic blood pressure, triglyceride, total cholesterol, HbA1c, FBG, 2 h-BG, fasting insulin and HOMA-IR (Table S1). In multivariate regression analyses, the results showed that age and HOMA-IR were two independent factors associated with circulating CTRP5, but there was no relationship between CTRP5 and other variables (Table S1). The multiple regression equation is $Y_{CTRP5} = 189.63 - 7.203X_{HbA1c} - 32.749X_{HOMA\text{-}IR}$.

Next, stepwise regression analyses were used to investigate the affecting factors of circulating CTRP5. When all study participants were included for analysis, the results showed that the main determinants of CTRP5 were HOMA-IR and HbA1c (Figure S1c).

Association of CTRP5 levels with the prevalence of type 2 diabetes

Multivariate logistic regression showed that CTRP5 levels in the circulation also correlated with the occurrence of type 2 diabetes, even after controlling for clinical and biochemical parameters (Table S2). Furthermore, CTRP5 levels in the circulation presented a linear trend and were associated with type 2 diabetes (Table S3). When circulating CTRP5 was divided into three tertiles in all study participants (tertile 1, <105.01 μg/L; tertile 2, 105.01–130.41 μg/L; tertile 3, >130.41 μg/L), the prevalences of developing type 2 diabetes were 78.37% for tertile 1, 62.16 for tertile 2 and 18.91% for tertile 3 (vs tertile 1, $P < 0.01$ or 0.05; Figure S2d). Finally, to predict the odds of developing type 2 diabetes, we carried out the analyses of the ROC curves. As shown in Figure 2, the AUC was 0.82 for type 2 diabetes (AUC_{T2DM}; sensitivity 75.0%, specificity 77.1%; Figure 2). The cut-off value of CTRP5 for predicting type 2 diabetes was 117 μg/L.

Table 1 | Main clinical features and circulating complement-1q tumor necrosis factor-α-related protein isoform 5 levels in the study participants

Variables	NGT (n = 116)	T2DM (n = 118)	P
Age (years)	54 ± 12.7	56 ± 9.1	NS
BMI (kg/m^2)	22.97 ± 2.35	24.87 ± 2.99	<0.01
FAT% (%)	28.45 ± 5.33	29.87 ± 6.24	NS
WHR	0.88 ± 0.09	0.92 ± 0.05	<0.01
SBP (mmHg)	119.23 ± 14.13	127.68 ± 11.24	<0.01
DBP (mmHg)	76.44 ± 10.19	76.25 ± 8.71	NS
FBG (mmol/L)	5.28 ± 0.42	8.66 ± 1.68	<0.01
2 h-BG (mmol/L)	6.16 ± 0.99	14.41 ± 2.84	<0.01
FIns (mU/L)	8.98 ± 3.63	14.03 ± 5.54	<0.01
HOMA-IR	2.01 (1.42–2.78)	5.21 (3.45–7.36)	<0.01
HbA1c (%)	5.45 ± 0.37	8.30 ± 0.95	< 0.01
TG (mmol/L)	1.29 ± 0.53	1.95 ± 0.83	<0.01
TC (mmol/L)	4.74 ± 0.90	4.97 ± 0.85	<0.05
HDL (mmol/L)	1.21 ± 0.19	1.10 ± 0.18	<0.01
LDL (mmol/L)	2.74 ± 0.80	2.76 ± 0.77	NS
FFA (mmol/L)	0.44 ± 0.14	0.46 ± 0.13	NS
CTRP5 (μg/L)	142.72 ± 34.24	105.59 ± 25.39	<0.01
CTRP5 (μg/L)†	140.31 ± 3.08	106.58 ± 2.88	<0.01

Data are mean ± standard deviation or median (interquartile range). †Data are mean ± standard error, adjustment for age, sex and body mass index (BMI). 2 h-BG, 2-h blood glucose after glucose overload; CTRP5, complement-1q tumor necrosis factor-α-related protein isoform 5; DBP, diastolic blood pressure; FAT%, the percentage of fat *in vivo*; FBG, fasting blood glucose; FFA, free fatty acid; FIns, fasting insulin; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; NS, not significant; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyeride; WHR, waist-to-hip ratio.

Effect of SGLTi treatment on CTRP5 levels in type 2 diabetes patients

As shown in Table S4, dapaglifozin administration for 3 months in type 2 diabetes patients led to a significant reduction in BMI, WHR, the percentage of body fat, blood pressure, HbA1c, FBG, 2 h-BG, fasting insulin and HOMA-IR ($P < 0.01$). However, after treatment, serum alanine transaminase, aspartate transaminase, serum creatinine, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and free fatty acid showed no change in these patients (Table S4). Of note, CTRP5 levels in the circulation were significantly reduced after SGLT2i treatment (from 99.72 ± 19.31 to 67.49 ± 33.02 μg/L, $P < 0.01$; Figure 1b).

DISCUSSION

The present study shows that circulating CTRP5 concentrations are markedly lower in newly diagnosed type 2 diabetes patients compared with controls. This result is analogous to the low Adipoq (a CTRP5 paralog) levels in type 2 diabetes patients, which have been widely acknowledged to be related to diabetes[27]. This finding is consistent with a recent study that reported the low levels of circulating CTRP5 in type 2 diabetes patients[28]. However, sample sizes in the study by Yan *et al.* were relatively small, and patients were treated with antidiabetic agents, insulin or other medications. In addition, patients with different disease durations and complications were included[28]. However, in a study of mice, Park *et al.* reported that obese and diabetic mice had higher circulating CTRP5 levels[15] than lean mice, whereas another study found that CTRP5 levels were not changed in *ob*/*ob* mice[20]. The discrepancy between mice and human studies is unclear, and might be due to the following reasons: (i) CTRP5 might play different roles in humans and mice, just as resistin plays different roles in humans and mice[29]; and (ii) type 2 diabetes in humans is a disease associated with multiple genes and environmental factors, whereas *ob*/*ob* and *db*/*db* mice are only caused by leptin deficiency. Therefore, the phenotype might be different because of the different genetic qualities.

Furthermore, in healthy individuals, circulating CTRP5 concentrations in the present study are lower than that reported by Emamgholipour *et al.*[30], but higher than that reported by Schwartze *et al.*[1] The discrepancy might be attributable to differences of the ethnic cohort, sample sizes, age of participants and/or assay method. Importantly, in the present study, the participants were age- and sex-matched, and a drug-naive population. However, follow-up studies are required to elucidate this issue.

Recently, CTRP5 has been found as a mediator of obesity, IR and metabolic syndrome [31]. Thus, we also analyzed the association of circulating CTRP5 and other metabolic markers. We found that CTRP5 correlated negatively with HbA1c, FBG

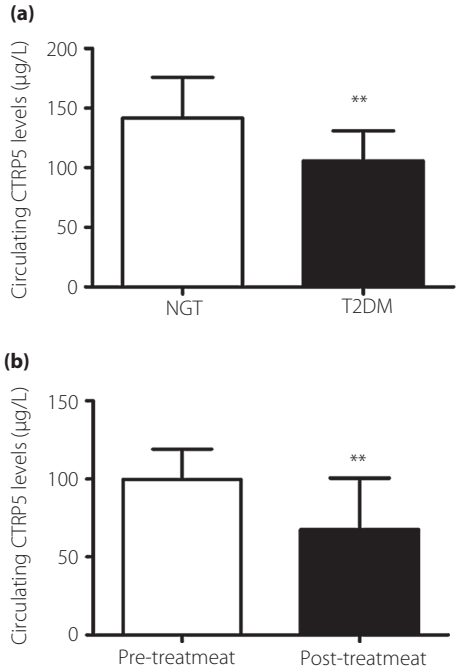

Figure 1 | Concentrations of circulating complement-1q tumor necrosis factor-α-related protein isoform 5 (CTRP5) in the study population. (a) Circulating CTRP5 levels in newly diagnosed type 2 diabetes and healthy participants. (b) Circulating CTRP5 levels pre- and post-treatment with SGLT2i in type 2 diabetes patients. Data are the mean ± standard deviation. $^{**}P < 0.01$ versus normal glucose tolerance (NGT) or pre-treatment. T2DM, type 2 diabetes.

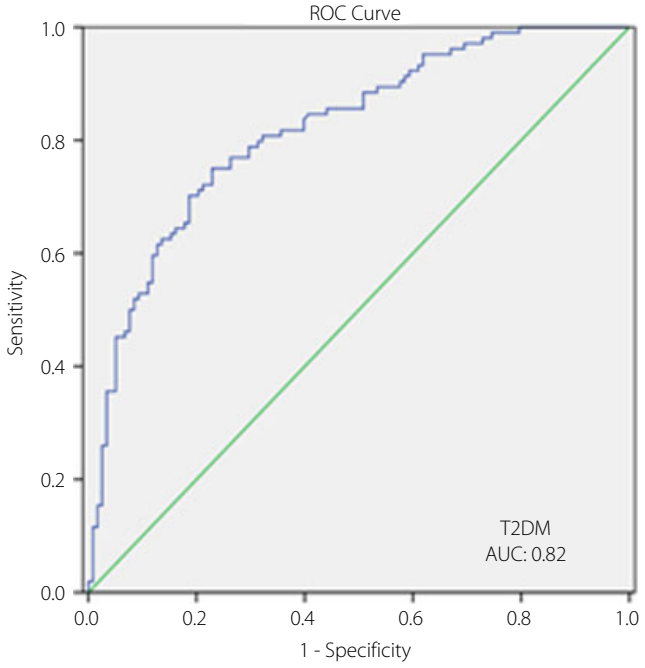

Figure 2 | Receiver operating characteristic (ROC) curve analyses were carried out for the prediction of type 2 diabetes according to the complement-1q tumor necrosis factor-α-related protein isoform 5 (CTRP5) levels. AUC, area under the receiver operating characteristic curve; T2DM, type 2 diabetes.

and 2 h-BG, suggesting a link between CTRP5 and glucose metabolism, and a possible role for CTRP5 in the development of diabetes. In previous studies, it has been reported that some members of the CTRP5 family are involved in the regulation of glucose and fatty acid metabolism[2,4,5,10,32,33]. Therefore, it is possible that CTRP5 serves as a regulator of glycometabolism.

Here, we also showed that CTRP5 concentrations were reduced in IR and type 2 diabetes states, and correlated negatively with HOMA-IR and HbA1c; ROC curves analysis also showed that circulating CTRP5 has a moderate effect to predict type 2 diabetes, suggesting that CTRP5 is associated with IR and type 2 diabetes. The result is consistent with the report by Emamgholipour *et al.*[30], but is inconsistent with that of Choi *et al.*[33], who found that there is no relationship between circulating CTRP5 and IR. In a high-fat diet-induced IR mice study, CTRP5-deficient mice showed attenuated hepatic steatosis and improved insulin action, suggesting a positive relationship between CTRP5 and IR[20]. In addition, IR is also affected by many other factors, including ethnicity, and genetic and nutritional status. Therefore, more studies of different populations are necessary to explore the association of CTRP5 with IR.

SGLT2i is a new class of antidiabetic agents with an insulin-independent mechanism[34]. SGLT2i is a transport protein for sodium–glucose cotransport in the kidney proximal tubule[35–37]. Therefore, SGLT2i, as a novel antidiabetic agent has two mechanisms that decrease blood glucose levels without increasing insulin secretion[38]. It also leads to weight loss through osmotic diuresis[39,40]. Recently, in a mice study, SGLT2i was found to improve IR *in vivo*[21]. In a previous study, we also reported that dapaglifozin treatment of type 2 diabetes significantly raised plasma zinc-alpha-2-glycoprotein and Adipoq (two insulin sensitizer) concentrations[41]. In addition, in an *in vitro* study, dapaglifozin treatment increased zinc-alpha-2-glycoprotein expression and secretion in HepG2 cells, whereas peroxisome proliferator-activated receptor-γ inhibitor co-treatment blocked the effects of dapaglifozin[41]. The present study showed that CTRP5 was closely correlated with IR. We thus investigated the impact of 12 weeks of dapaglifozin therapy on CTRP5 concentrations in type 2 diabetes patients. Consistent with previous reports, we showed that dapaglifozin reduced the HbA1c, FBG, 2 h-BG and insulin levels, and HOMA-IR, indicating improved glucose metabolism and increased insulin sensitivity in tissues. After SGLT2i administration for 12 weeks, circulating CTRP5 levels significantly decreased in type 2 diabetes patients, despite improving IR. Therefore, this result suggests that CTRP5 can only be used for the diagnosis of newly diagnosed type 2 diabetes patients, but not for the evaluation of the therapeutic

effect. This fact might limit its possible clinical application value. We speculate that there are several explanations for this finding: (i) SGLT2i might inhibit CTRP5 expression and secretion in peripheral tissues; (ii) SGLT2i might promote the degradation or elimination of CTRP5; or (iii) SGLT2i treatment might increase other cytokines in circulation, such as Adipoq and fibroblast growth factor 21[21], which inhibited CTRP5 secretion and release into circulation. In addition, SGLT2i improves the IR state, thereby reducing the compensatory secretion of CTRP5 under IR. However, the precise mechanism (s) by which SGLT2i increases insulin sensitivity and decreases circulating CTRP5 levels remains unclear.

Because the mechanism of the role of SGLT2i is different from other hypoglycemic drugs, it is not clear whether other drugs can lead to the decrease of circulating CTRP5 levels. Although bivariate correlation analyses showed that serum CTRP5 is negatively correlated with HOMA-IR and blood glucose level, the decrease of HOMA-IR and blood glucose after SGLT2i treatment indicates that these factors could not directly cause the increase of circulating CTRP5. Therefore, in diabetes patients, there might be other causes leading to decreased CTRP5 expression, such as lipid metabolism disorders or changes in other adipokines. Further in-depth studies are necessary.

The present study had some limitations. First, the nature of a cross-sectional study is not allowed to decide causation. Second, the interventional study was an open-label, self-controlled trial without a placebo-controlled group, thus weakening the stringency of the results. Third, individuals recruited in the study came from routine medical checkups, so the participants did not fully represent the overall situation of type 2 diabetes and a healthy population. Therefore, a selective bias is noteworthy. Fourth, this study was carried out in a Chinese population. Therefore, the results might not apply to other ethnicities. Fifth, circulating CTRP5 concentrations were determined by a single measurement, and it might not reflect the alterations of CTRP5 from prediabetes to diabetes. Thus, it is important to measure CTRP5 levels at different stages of IR or type 2 diabetes. Nevertheless, data from the present study sufficiently show the relationship among CTRP5, IR and type 2 diabetes, and suggest that alterations in circulating CTRP5 levels might play a role in the development of IR and diabetes.

In conclusion, as a primary outcome of the present study, we showed that CTRP5 levels in circulation were markedly decreased in newly diagnosed type 2 diabetes patients and correlated with IR. As a secondary outcome, we found that after 12 weeks of SGLT2i treatment, serum CTRP5 levels in type 2 diabetes patients were significantly reduced accompanied with improved IR. Therefore, we conclude that CTRP5 is likely a marker for type 2 diabetes in humans.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Flow diagram.

Figure S2 | (a) Distribution of circulating concentration of complement-1q tumor necrosis factor-α-related protein isoform 5 (CTRP5) in 116 healthy individuals. (b) Circulating CTRP5 levels according to the homeostasis model of assessment of insulin resistance (HOMA-IR). (c) All factors and stepwise multiple regression analyses of the circulating CTRP5 in the entire study population. The circles correspond to the regression coefficients (β) and the error bars indicate the 95% confidence interval of β. R^2, coefficient of determination. (d) Prevalence of elevated type 2 diabetes in different quartiles of CTRP5.

Table S1 | Linear regression analysis of variables associated with circulating complement-1q tumor necrosis factor-α-related protein isoform 5 levels in the study population.

Table S2 | Association of circulating complement-1q tumor necrosis factor-α-related protein isoform 5 with type 2 diabetes in fully adjusted models.

Table S3 | Row mean scores and Cochran–Armitage trend test of the impact of plasma complement-1q tumor necrosis factor-α-related protein isoform 5 level on type 2 diabetes.

Table S4 | Clinical characteristics pre- and post-treatment with dapaglifozin in type 2 diabetes patients.