JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

C1q tumor necrosis factor-related protein 4 is associated with coronary artery disease in patients with type 2 diabetes

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Keywords
C1q tumor necrosis factor-related protein 4, Coronary artery disease, Type 2 diabetes mellitus

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J Diabetes Investig 2022; 13: 1723–1731

doi: 10.1111/jdi.13842

ABSTRACT

Aims/Introduction: To evaluate the correlation of circulating C1q tumor necrosis factor-related protein 4 (CTRP4) with coronary artery disease (CAD) in type 2 diabetes mellitus patients.

Methods: A total of 240 individuals with type 2 diabetes mellitus were enrolled in our center between January 2020 and December 2020. They were assigned into two groups, including the CAD and non-CAD groups, based on coronary angiography or computed tomography angiography findings. Serum CTRP4 levels were detected by an enzyme-linked immunosorbent assay kit. The association of CTRP4 with CAD was determined by logistic regression analysis. The predictive value of CTRP4 for CAD was calculated by receiver operating characteristic curve analysis.

Results: Median serum CTRP4 amounts were markedly elevated in the CAD group in comparison with the non-CAD group (10.37 vs 3.75 ng/mL, $P < 0.01$). Binary logistic regression showed that CTRP4 was associated with CAD and even the amount of coronary artery lesions ($P < 0.05$). In receiver operating characteristic curve analysis, the area under the receiver operating characteristic curve was greater for CTRP4 compared with HbA1c or CRP (0.87 vs 0.74, 0.87 vs 0.80, $P < 0.01$). The area under the curve for CTRP4 and glycated hemoglobin in combination was larger than that obtained for CTRP4 combined with CRP (0.91 vs 0.87, $P < 0.01$). According to the maximum Youden index criteria, the optimal cut-off of CTRP4 was 5.42 ng/mL, which yielded a sensitivity of 84.4% and a specificity of 76.7% in predicting CAD in type 2 diabetes mellitus patients.

Conclusions: Serum CTRP4 levels are positively correlated with CAD occurrence and severity. Combining CTRP4 and glycated hemoglobin has a better predictive value for CAD in type 2 diabetes mellitus patients.

INTRODUCTION

Type 2 diabetes mellitus represents a disorder with chronic metabolic alterations, which features hyperglycemia resulting from insulin resistance and β-cell impairment[1]. With the Westernization of lifestyles, and increased obesity prevalence and average life expectancy, type 2 diabetes mellitus prevalence is growing rapidly[2,3]. However, cardiovascular disease constitutes the top cause of death in diabetes patients[4–8]. Type 2 diabetes mellitus is considered an important risk factor for cerebrovascular, cardiovascular and renal diseases[9,10]. Evidence shows coronary artery disease (CAD) and myocardial infarction (MI) are two- to fourfold more likely to occur in patients with diabetes than in patients without diabetes[11]. Indeed, approximately 70% of patients with type 2 diabetes aged ≥65 years die from CAD[11]. Individuals with type 2 diabetes mellitus and no previous CAD have a similar risk of cardiovascular death as those with previous MI over 7 years follow up[12,13]. Mounting evidence shows inflammation has a critical function in impaired endothelial function and atherosclerosis development[14,15]. It was shown that

†These authors contributed equally to this article.
Received 1 February 2022; revised 15 May 2022; accepted 20 May 2022

type 2 diabetes mellitus independently elevates atherosclerosis prevalence, inflammatory cell infiltration and plaque necrosis if coexisting with CAD[16,17].

The C1q tumor necrosis factor-related protein (CTRP) family, containing 15 members[18], was first identified by Harvey Lodish *et al.* in 2004[19]. It is a highly conserved superfamily and homologous to adiponectin[19]. It plays important roles in glucose metabolism[20], fatty acid oxidation[21] and aldosterone production[22]. Unlike other family members, CTRP4 is the only member of the CTRP superfamily that contains two globular C1q domains, endowing it with diverse functions[23]. CTRP4 is found in various tissues, such as fat, brain and bone marrow stem cells, and is also present in circulation[24]. Current studies have found CTRP4 is involved in food intake control, tumorigenesis and inflammation, and has an impact on glucose and lipid metabolism[25–29]. In addition, an increasing number of reports showed associations of CTRPs with CAD, emphasizing their reference value for assessing the progression and prognosis of CAD[30–35]. Therefore, we speculated that CTRP4 might be associated with CAD risk in type 2 diabetes mellitus patients, but data supporting this notion are unavailable. In the present study, we collected the clinical data of type 2 diabetes mellitus patients with or without CAD in our center, aiming to determine the predictive value of CTRP4 for CAD in patients with type 2 diabetes.

MATERIALS AND METHODS

Study design and participants

This was a cross-sectional study. We carried out our study in Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, which was designed to collect detailed clinical data of type 2 diabetes mellitus patients. A total of 456 individuals diagnosed with type 2 diabetes mellitus between January 2020 and December 2020 were recruited in the study. Patients who first received coronary angiograms or computed tomography angiography images or/and had a history of CAD were included, and a total of 333 patients were initially selected for the study. Individuals with acute infection, acute stress state, malignant tumors, severely impaired liver function (alanine transaminase or aspartate aminotransferase threefold the upper limit of normal reference range), severely impaired kidney function (glomerular filtration rate 30 mL/min/1.73 m^2), chronic inflammatory diseases or connective tissue diseases were excluded. For these patients, coronary angiograms or computed tomography angiography images were evaluated by an experienced cardiologist blinded to the diagnoses of these patients. Patients with one or more major coronary artery stenoses ≥50% or a history of CAD were assigned to the CAD group. Finally, 240 patients were included, and assigned to two groups, including the non-CAD (n = 60) and CAD (n = 180) groups (Figure 1).

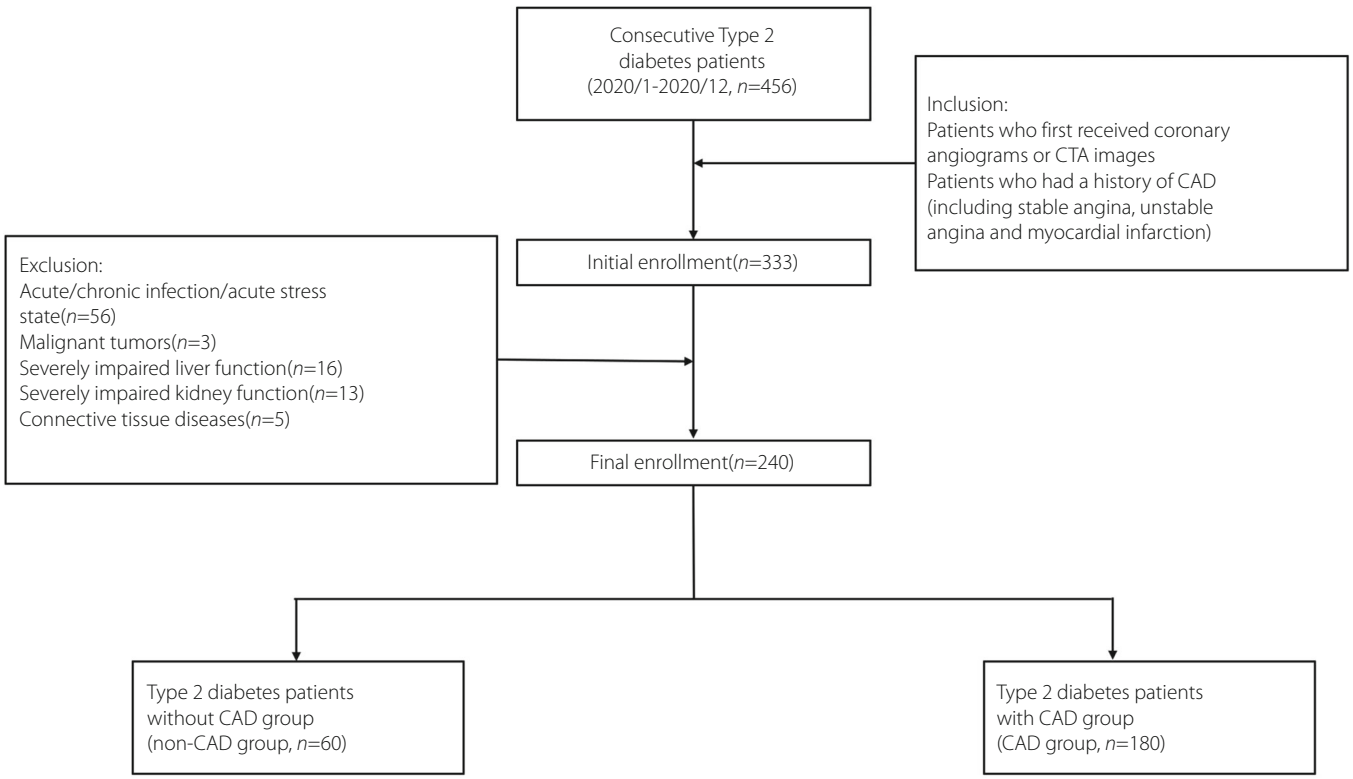


Figure 1 | Flow diagram of the research process. CAD, coronary artery disease; CTA, computed tomography angiography.

The present trial had approval from Shanghai University of Traditional Chinese Medicine Affiliated Putuo hospital's institutional review board based on the second Helsinki Declaration. Each participant provided signed informed consent, all information and data anonymity were maintained.

Anthropometric and laboratory investigations

We measured the anthropometric data and biochemical parameters of all participants at the time of admission. A mercury sphygmomanometer was utilized to measure blood pressure twice with the participants in the supine position, and the readings were averaged. Height and weight of all patients were measured using standard methods. We calculated body mass index (BMI; kg/m^2) using weight divided by height squared. After fasting for at least 8 h, 5 mL of blood was obtained the next morning from each patient. Fasting blood glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein and postprandial blood glucose (PBG) amounts were detected on a Beckman Coulter AU5800 automatic biochemical analyzer (Brea, CA, USA). Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (Tosoh Automated Glycohemoglobin Analyzer HLC-723G11, Shunan, Japan). We calculated the estimated glomerular filtration rate by using the Chronic Kidney Disease Epidemiology Collaboration method[36]. Serum CTRP4 concentrations were assessed with a specific enzyme-linked immunosorbent assay kit (Raybiotech, Norcross, GA, USA) at the time of coronary imaging.

Hypertension was defined as systolic and/or diastolic blood pressure ≥140 and/or ≥90 mmHg, respectively[37], self-reported history of hypertension or current treatment with antihypertensives. Type 2 diabetes mellitus was considered with FBG ≥7.0 mmol/L, 2-h PBG ≥11.1 mmol/L and/or HbA1c ≥6.5% based on criteria suggested by the American Diabetes Association in 2021[38], or current treatment with antidiabetic drugs. The criteria of CAD were defined as >50% stenosis at least one major coronary artery (including left main coronary artery, anterior descending coronary artery, circumflex branch and right coronary artery). A stenosis ≥50% was considered as single-vessel disease, two stenosis ≥50% was considered as double-vessel disease and more than two stenosis ≥50% was defined as triple-vessel disease. The history of CAD was defined as a history of stable angina or acute coronary syndromes, including unstable angina and myocardial infarction.

Statistical analysis

We used the Kolmogorov–Smirnov test to assess the distribution of continuous variables. Normally distributed continuous variables were expressed as the mean ± standard deviation, abnormally distributed variables as the median (interquartile range [IQR]) and categorical variables as the number (percentage), respectively. For comparisons between two groups, the independent samples *t*-test was applied for normally distributed continuous variables, and the Mann–Whitney *U*-test was used for skewed data. The Kruskal–Wallis test was used to test differences in medians among three groups. For categorical data, the χ^2-test or Fisher's exact test were used to test the differences between groups. According to the tertiles of CTRP4 levels, the participants were divided into three groups: tertile 1, ≤5.45 ng/mL; tertile 2, 5.45–11.68 ng/mL; and tertile 3, ≥11.68 ng/mL. Binary logistic regression analysis was carried out to assess the correlation between CTRP4 and CAD. Variables that were statistically significant between the CAD group and non-CAD group or clinically important risk factors for CAD, although they were not statistically significant, were included in the binary logistic regression. Receiver operating characteristic (ROC) curve analysis was carried out to examine CTRP4 for sensitivity and specificity in predicting CAD in patients with type 2 diabetes. The optimal cut-off in each ROC curve was based on maximal Youden Index criteria. The areas under the curves (AUCs) for CTRP4 and/or other clinical parameters were determined with MedCalc statistical software (Ostend, Belgium). Two-sided $P < 0.05$ showed statistical significance. The SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was utilized for data analysis.

RESULTS

Baseline patient features

The clinicopathological features and biochemical indexes of the 240 patients are shown in Table 1. The proportions of male, hypertension and smoking cases were higher in the CAD group in comparison with the non-CAD group ($P < 0.05$). In addition, patients in the CAD group had higher levels of FBG, PBG, HbA1c and CRP compared with the non-CAD group ($P < 0.01$). Median serum CTRP4 amounts were markedly reduced in the non-CAD group compared with the CAD group (3.75 vs 10.37, $P < 0.01$). Age, BMI, estimated glomerular filtration rate, proportion of participants who drank alcohol and participants using antidiabetic drugs were similar in both groups. In the present study, lipids including LDL-C were lower in the CAD group compared with the non-CAD group, although not reaching statistical significance. This might be due to the higher use of statin in the CAD group (97.2% vs 76.7%, $P < 0.01$).

CTRP4 is associated with CAD in type 2 diabetes mellitus patients

As shown in Table 2, total CTRP4 amounts were positively correlated with CAD in type 2 diabetes mellitus patients after adjusting for sex, age, BMI, hypertension, smoking status and LDL-C (odds ratio [OR] 1.58, 95% confidence interval [CI] 1.35–1.84), as well as further adjustment for HbA1c (OR 1.56, 95% CI 1.33–1.83) and CRP (OR 1.54, 95% CI 1.26–1.88). From the lowest serum CTRP4 tertile to the highest, CAD risk in type 2 diabetes mellitus patients significantly rose. In comparison with tertile 1, ORs in tertiles 2 and 3 of CTRP4 were 8.68 (95% CI 3.72–20.26) and 110.92 (95% CI 14.31–859.80) in model 1, respectively. The corresponding ORs were 8.64 (95%

Table 1 | Baseline clinical characteristics of the participants

Clinical characteristic	Non-CAD group (n = 60)	CAD group (n = 180)	P-value
Age (years)	57.90 ± 10.52	59.43 ± 9.35	0.288
Male (%)	35 (58.3%)	136 (75.6%)	**0.014**
BMI (kg/m^2)	26.75 ± 3.29	27.37 ± 5.04	0.275
Hypertension (%)	37 (61.7%)	143 (79.4%)	**0.009**
Smoking (%)	40 (66.7%)	148 (82.2%)	**0.018**
Drinking (%)	38 (63.3%)	123 (68.3%)	0.527
TC (mmol/L)	5.34 (4.31–5.91)	4.84 (4.06–5.89)	0.120
TG (mmol/L)	1.97 (1.39–3.22)	1.78 (1.19–2.58)	0.139
HDL-C (mmol/L)	1.13 (0.91–1.30)	1.10 (0.91–1.28)	0.579
LDL-C (mmol/L)	3.60 (2.81–4.31)	3.19 (2.69–4.00)	0.051
eGFR (mL/1.73 m^2/min)	98.88 ± 15.26	95.96 ± 14.79	0.191
CRP (mg/L)	3.72 (1.86–6.37)	9.44 (5.52–12.97)	**0.000**
FBG (mmol/L)	7.15 (6.40–8.00)	9.10 (7.00–11.88)	**0.000**
PBG (mmol/L)	11.20 (9.93–14.03)	15.35 (12.23–18.78)	**0.000**
HbA1c (%)	7.20 (6.60–8.30)	9.35 (7.23–11.58)	**0.000**
CTRP4 (ng/mL)	3.75 (2.52–5.38)	10.37 (6.71–15.71)	**0.000**
Medications			
Aspirin (%)	48 (80.0%)	172 (95.6%)	**0.001**
Statin use (%)	46 (76.7%)	175 (97.2%)	**0.000**
Antidiabetic (%)	53 (88.3%)	156 (86.7%)	0.739

Data were expressed as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for abnormally distributed variables and number (%) for category variables. For comparisons between groups, the independent samples t-test was applied for normally distributed continuous variables, and Mann–Whitney U-test was used for skewed data. For categorical data, χ^2-test or Fisher's exact test were used to test the differences between groups. Statin includes rosuvastatin, simvastatin, pravastatin and so on. Antidiabetic medications include metformin, sulfonylureas, glitazones, glinides and so on. Bold values indicate the comparisons between two groups were statistically significant. BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBG, postprandial blood glucose; TC, total cholesterol; TG, triglyceride.

Table 2 | Association of C1q tumor necrosis factor-related protein 4 levels with coronary artery disease in patients with type 2 diabetes mellitus

CTRP4	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Total	1.58	1.35–1.84	1.56	1.33–1.83	1.54	1.26–1.88
Tertiles						
2nd	8.68	3.72–20.26	8.64	3.40–21.90	6.83	2.38–19.61
3rd	110.92	14.31–859.80	126.27	14.93–1067.91	63.84	4.99–817.52
P trend	$P < 0.001$		$P < 0.001$		$P < 0.001$	
SD	19.40	7.15–52.64	18.22	6.49–51.16	16.74	4.59–60.98

Data were obtained using a binary logistic regression model. Model 1 was adjusted for sex, age, body mass index, hypertension, smoking status and low-density lipoprotein cholesterol. Model 2 was adjusted for sex, age, body mass index, hypertension, smoking status, low-density lipoprotein cholesterol and glycated hemoglobin. Model 3 was adjusted for sex, age, body mass index, hypertension, smoking status, low-density lipoprotein cholesterol, glycated hemoglobin and C-reactive protein. Tertile 1 of C1q tumor necrosis factor-related protein 4 (CTRP4) levels was taken as a reference in the binary logistic regression analysis. CI, confidence interval; SD, standard deviation.

CI 3.40–21.90) and 126.27 (95% CI 14.93–1067.91) in adjusted model 2, and 6.83 (95% CI 2.38–19.61) and 63.84 (95% CI 4.99–817.52) in adjusted model 3, respectively (all P for trend <0.001). Each one standard deviation increase in CTRP4 (ng/mL) was associated with a 19.40-fold (95% CI 7.15–52.64) increase of CAD risk after adjustment for sex, age, BMI, hypertension, smoking status and LDL-C (model 1). After further adjustment for HbA1c and CRP, similar results were obtained (OR 18.22, 95% CI 6.49–51.16, model 2; OR 16.74, 95% CI 4.59–60.98, model 3).

Relationship between CTRP4 and number of coronary artery lesions in type 2 diabetes mellitus patients

Serum CTRP4 concentration was positively correlated with the number of coronary artery lesions in type 2 diabetes mellitus patients. As shown in Figure 2, the median CTRP4 levels in the single, double and multiple vessel disease groups were 5.45 (IQR 3.82–6.82), 10.37 (IQR 8.79–13.32) and 17.64 (IQR 15.65–20.73) ng/mL, respectively, showing significant differences ($P < 0.01$).

Predictive value of CTRP4 for CAD in type 2 diabetes mellitus patients

In descending order, the AUCs for CTRP4, CRP and HbA1c were 0.87, 0.80 and 0.74, respectively. The AUC based on CTRP4 was higher than that based on CRP or HbA1c, and the differences were statistically significant (all $P < 0.01$). The AUC for CTRP4 and HbA1c in combination was 0.91, which were larger than the model based on the combination of CTRP4 and CRP ($P < 0.01$). Furthermore, it was similar to the model based on the combination of CTRP4 and other indexes, including sex, age, smoking status, hypertension, LDL-C, BMI, HbA1c and CRP ($P > 0.05$). ROC analysis showed that a threshold of 5.42 ng/mL for CTRP4 was the best cut-off for detecting CAD in type 2 diabetes mellitus patients, with a sensitivity of 84.4% and a specificity of 76.7% (Figure 3).

DISCUSSION

Epidemiological evidence suggests type 2 diabetes mellitus as an established risk factor for CAD, and patients with diabetes have a higher prevalence of CAD[39]. The major underpinning mechanism of CAD is atherosclerosis[40], and inflammation caused by pro-inflammatory cytokines is critical in atherogenesis. In addition, abnormal glucose and lipid metabolism induce CAD development by affecting the degree of inflammation, regulatory pathways, final product composition and atherosclerotic plaque formation[41,42]. Previous studies[43–45] also reported that HbA1c was closely associated with CAD and could be used as a marker of CAD. The higher HbA1c levels could predict higher coronary artery disease burden. The present study also showed that HbA1c had a good predicative value for CAD in patients with type 2 diabetes. Furthermore, the predicative value of CTRP4 combined with HbA1c was better than that of CTRP4 combined with CRP.

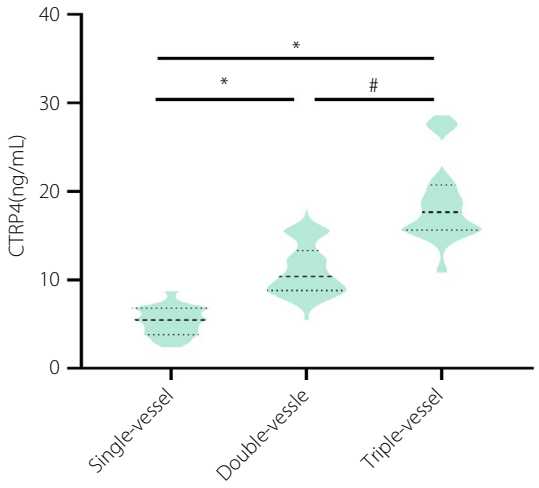
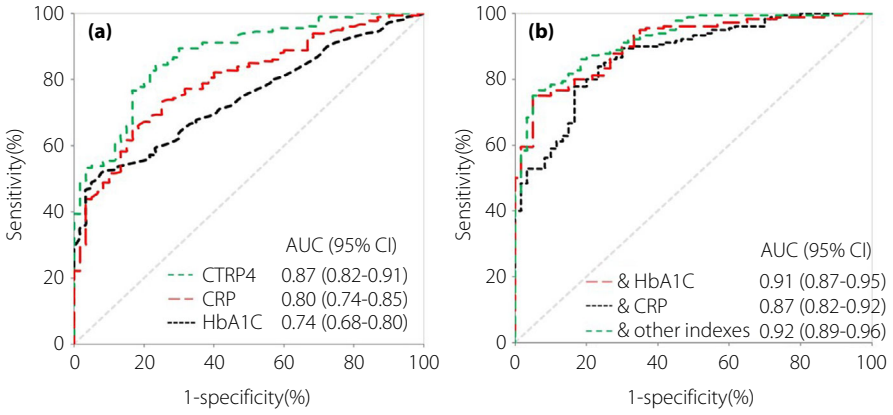


Figure 2 | Relationship between C1q tumor necrosis factor-related protein 4 (CTRP4) concentration and the number of coronary artery lesions in patients with type 2 diabetes mellitus. Data were analyzed by the Kruskal–Wallis test. *$P < 0.05$ compared with group A; #$P < 0.05$ compared with group B.

CTRPs, including CTRP1-CTRP15, are secreted adipokines, many of which are associated with type 2 diabetes mellitus and CAD. For example, CTRP1 regulates glycolipid metabolism[46], stimulates the production of adhesion molecules and inflammatory cytokines, and promotes the generation of macrophages-derived foam cells[33,47–50]. CTRP3 exerts a protective effect against inflammatory and apoptotic signals in the development of CAD[30,51]. It also suppresses the progression of CAD by improving insulin resistance, enhancing glucose uptake and reducing gluconeogenesis in hepatocytes[52,53]. CTRP9 protects from CAD by inhibiting the expression of adhesion molecules and pro-inflammatory cytokines, promoting vasodilation, and increasing the stability of atherosclerotic plaques[35,54–56]. Overexpression of CTRP9 increases insulin sensitivity, and decreases fasting insulin and FBG amounts[57,58]. CTRP12 and CTRP13 exert beneficial effects on CAD by suppressing the inflammatory response, decreasing plaque formation and macrophage accumulation, and regulating glucose and insulin metabolism[59–61].

CTRP4, the only CTRP with two C1q globular domains, is mainly expressed in brain tissue, adipose tissue and bone marrow stem cells, and is also found as a circulating protein in the blood[24]. It has many physiological functions associated with inflammation and metabolism, but its role is not fully understood. Luo *et al.*[28] reported that CTRP4 could mitigate the symptoms of colitis and inhibit tumorigenesis associated with colitis in mice. Sarver *et al.*[29] found CTRP4 suppression increases serum cholesterol levels and induces glucose intolerance in male mice. Ye *et al.*[62] found that CTRP4 ameliorates leptin resistance by inactivating microglial cells and inhibiting hypothalamic inflammation through the nuclear factor-κB pathway. Duan *et al.*[63] showed that CTRP4 deficiency activates caspase-1/interleukin-1β inflammatory signaling in pre-eclampsia rat models. Interestingly, Li *et al.*[25] found that CTRP4 reduces food intake by inducing the signal transducer and activator of transcription 3 and nuclear factor-κB pathways. A recent study reported by Dai *et al.*[64] showed that CTRP4 amounts are lower in non-ACS cases compared with ACS patients. However, Liu *et al.*[65] found that serum CTRP4 levels were decreased in newly diagnosed type 2 diabetes mellitus patients compared with healthy controls. These controversial studies showed that CTRP4 plays distinct roles in inflammatory pathways based on cell context, cell type and/or



	Maximum Youden index		
A	Cut-offs	Sensitivity(%)	Specificity(%)
CTRP4(ng/mL)	5.42	84.4	76.7
HbA1c (%)	9.25	52.2	91.7
CRP (mg/L)	5.89	73.3	75.0
B			
&HbA1c	0.81	75.0	95.0
&CRP	0.70	77.8	83.3
& other indexes	0.84	75.0	95.0

Figure 3 | Receiver operating characteristic curves for coronary artery disease in patients with type 2 diabetes mellitus. (a) The predictive value of a single indicator for coronary artery disease. (b) The predictive value for C1q tumor necrosis factor-related protein 4 (CTRP4) combined with other indicators of coronary artery disease. Other indexes included sex, age, smoking status, hypertension, Low-density lipoprotein cholesterol, body mass index, glycated hemoglobin (HbA1c) and C-reactive protein (CRP). AUC, area under the curve; CI, confidence interval.

receptor(s)[24]. The present study found that high serum CTRP4 levels were strongly correlated with the occurrence of CAD in patients with type 2 diabetes, which was consistent with the report by Hu Xiang-wen[66]. It might be explained that the functions of CTRP4 are context-dependent and can play a dual role in inflammation. It might act as an anti-inflammatory role in the hypo-inflammatory state, while play a pro-inflammatory effect in the hyper-inflammatory state. Another explanation might be that CTRP4 is a compensatory response against inflammation in type 2 diabetes patients with CAD. However, the mechanisms underpinning the relationship between CTRP4 and CAD remain unknown, and need to be further investigated.

The strength of the present study was that it was among the first examining the association of CTRP4 with CAD and determining the value of CTRP4 in predicting CAD risk in type 2 diabetes mellitus patients. However, the limitations of this work should be acknowledged. First, the sample size was relatively small, and studies with larger samples carried out in multiple centers are required in the future. Second, it was a cross-sectional study, and prospective cohort trials are required to assess the correlation of CTRP4 with CAD. Finally, some established inflammatory cytokines related to atherosclerosis could be examined; for example, interleukin-6, interleukin-1β and tumor necrosis factor-α, to further characterize the influence of CTRP4 on CAD in type 2 diabetes mellitus patients.

In conclusion, serum CTRP4 concentration is positively correlated with CAD occurrence and severity. The combination of CTRP4 and HbA1c showed a better predicative value for CAD in type 2 diabetes mellitus patients. The current findings show that CTRP4 might have a critical function in CAD pathophysiology, and could be used as a novel biomarker of CAD in type 2 diabetes mellitus patients.

ACKNOWLEDGMENTS

We thank all the participants and the research team involved in the present project. The present study was supported by Clinical Characteristic of Health System in Putuo District, Shanghai (2020tszk01) and Shanghai Key Medical Specialities (ZK2019B16).

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This study was approved by the institutional review board of Putuo hospital, Shanghai University of Traditional Chinese Medicine.

Registry and the registration no. of the study/trial: 5 November 2020 and A-2020-38-1.

Informed consent: Written informed consent was received from each participant.
Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The original data used in this study are available from the corresponding author upon request.

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