ORIGINAL RESEARCH

Role of C1q/TNF-Related Protein 6 for the Evaluation of Coronary Heart Disease Associated with Type 2 Diabetes

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Objective: Coronary artery disease (CAD) and type 2 diabetes (T2DM) are closely associated with increased rate of death. C1q/TNF-related protein 6 (CTRP6) is a novel adipocytokine which plays an important role in glucose and lipid metabolism. Little is known about the function of CTRP6 in CAD and T2DM patients. Herein, we aimed to study the association of CTRP6 level with CAD and T2DM.

Methods: This study included 51 CAD, 44 CAD+T2DM and 65 non-CAD+T2DM patients from Affiliated Aoyang Hospital of Jiangsu University. Serum CTRP6 concentrations were detected by ELISA. Multiple logistic regression was used to analyze the association of serum CTRP6 with CAD and T2DM.

Results: Serum CTRP6 concentrations were significantly lower in CAD patients than controls. However, there is no significant statistical difference between CAD+T2DM patients and non-CAD+T2DM patients. Serum CTRP6 was negatively correlated with low-density lipoprotein cholesterol (LDL-C) ($\rho=-0.2769$, p=0.028) in controls. Serum CTRP6 was positively correlated with age ($\rho=0.4121$, p=0.0027), systolic blood pressure (SBP) ($\rho=0.4012$, p=0.0035), Creatinine ($\rho=0.3295$, p=0.0194), uric acid (UA) ($\rho=0.3386$, p=0.0162), and left ventricular end diastolic diameter (LVD) ($\rho=0.4277$, p=0.0042) and negatively correlated with ejection fraction (EF) ($\rho=-0.3237$, p=0.0342) in CAD patients. Serum CTRP6 was negatively correlated with high-density lipoprotein cholesterol (HDL-C) ($\rho=-0.3164$, p=0.0387) in CAD+T2DM patients. Multiple logistic regression showed that the decrease of CTRP6 was significantly related to the increased prevalence of CAD. What is more, CTRP6 increased prevalence of T2DM in CAD patients.

Conclusion: Lower serum CTRP6 could be a risk factor of CAD. However, higher circulating CTRP6 associated with the increased prevalence of T2DM in CAD patients.

Keywords: CTRP6, coronary artery disease, type 2 diabetes, adipokine, CTRP, risk factor

Introduction

Cardiovascular mortality has fallen in developed countries during the past four decades.[1] However, mortality has persistently increased in China. Based on epidemiological survey, there are 330 million cardiovascular disease (CVD) patients in China.[2] CVD continues to be a leading cause of death around the world.[3] Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia and impaired islet secretion. By 2025, the number of DM patients is expected to rise to 300 million around the world.[4] DM is now the seventh leading cause of death in the worldwide.[5] T2DM accounts for more than 90% of the total number of DM. It has far-reaching effect on the health and economy.[6] Previous study showed that T2DM had a higher mortality rate for CVD compared with controls.[7] Hence, we should pay more attention to patients with CVD and T2DM.

C1q/TNF-related protein (CTRP) family is a newly identified and highly conserved family which contains 15 members (CTRP1-CTRP15).[8] Each CTRP has its own specific distribution in vivo and exerts diverse functions.[9] CTRP family has attracted a lot of attention because it plays an important role in energy homeostasis, inflammation and myocardial protection and vasodilation.[10] CTRP6 is a novel adiponectin including 259 amino acids. It contains four different domains, comprising signal peptide, short N-terminal variable region, collagen domain and C-terminal C1q domain.[11] CTRP6 expressed abundantly in adipose tissue, heart, brain, and so on.[12] Previous studies showed that CTRP6 participated the regulation of endothelial cell function angiotensin II–induced hypertension.[13] Wang et al reported that CTRP6 was related with insulin resistance. Circulating CTRP6 levels increased in T2DM patients in Chinese population.[14]

According to previous researches concerning the relationship between CTRP6 and endothelial cell function, circulating CTRP6 might be a potential marker of CAD. The association between CTRP6 and T2DM has been evaluated. However, the role of CTRP6 in CAD has not been well described. Accordingly, in this study, we aimed to assess the association between CTRP6 levels and CAD. Furthermore, we evaluated CTRP6 levels in CAD patients with or without T2DM.

Methods

Study Subjects

This is a case–control study. A total of 160 patients including 51 CAD, 44 CAD+T2DM and 65 non-CAD+T2DM patients were recruited from Affiliated Aoyang Hospital of Jiangsu University. Coronary artery was assessed by coronary angiography. CAD was diagnosed by ≥50% stenosis in at least one main coronary artery or its major branch, or a history of revascularization by percutaneous coronary intervention or angina pectoris. Angina pectoris was defined as effort substernal chest discomfort relieved by rest with dynamic changes in electrocardiogram. Patients with an acute infection, severe hepatic or renal dysfunction, malignancy, a history of coronary artery bypass grafting (CABG) were excluded from the study. The study was approved by the Ethics Committee of Affiliated Aoyang Hospital of Jiangsu University. We have obtained informed consent from human subjects.

Data Collection

Fasting blood samples were collected after admission. Reagents for measuring neutrophil (NE), lymphocyte (LY), hemoglobin (HB), platelet (PLT), glucose, albumin, triglyceride (TG), total cholesterol (TC), apolipoprotein A (ApoA), apolipoprotein B (ApoB), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, urea nitrogen (BUN), uric acid (UA), potassium, calcium, phosphate, free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were obtained from Sekisui Diagnostic Ltd. We choose Cusabio's human CTRP6 ELISA kit. The measurement was performed in accordance with the manufacturer's instructions. Calibrator and control reagents were performed according to the laboratory's protocols. Gensini score was calculated according to previous study.[15] Left atrium (LA), left ventricular end diastolic diameter (LVD), and ejection fraction (EF) were measured in color Doppler echocardiography.

Statistical Analysis

All statistical analyses were completed with STATA 14.0. We used Kolmogorov–Smirnov test to test the normality of continuous variables. Normally distributed data and non-normally distributed data were shown as median (25th-75th). Independent samples *t*-test and Mann–Whitney *U*-test were used to compare continuous variables separately. Categorical variables were shown as frequencies and percentages. χ^2 test was applied to analyze categorical variables. Kruskal Wallis test and one-way ANOVA were used for multiple testing among groups. Spearman correlation analysis was used to analyze the association of CTRP6 with other factors. Logistic regression models were performed among CAD, CAD +T2DM, and non-CAD+T2DM patients. As a common rule, a variance inflation factor (VIF) >5 was considered for the presence of multicollinearity. These variables were excluded from Logistic regression models.

Results

General Clinical Characteristics of the Population

This study included 160 subjects. Subjects were divided into 3 groups. The clinical characteristics of the population are shown in Table 1. In total, 115 males and 55 females were included. The median and interquartile range (IQR) age of the subjects were 60 (55–69) in controls, 65 (57–71) in CAD, and 64.5 (55–73) in CAD+T2DM (P=0.001). There was no significant difference among age, body mass index (BMI), Gensini Score, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking history, drinking history, neutrophil (NE), hemoglobin (HB), platelet (PLT), albumin, trigly-ceride (TG), total cholesterol (TC), apolipoprotein B (Apo B), low-density lipoprotein cholesterol (LDL-C), creatinine, urea nitrogen (BUN), uric acid (UA), potassium, free triiodothyronine (FT3), thyroid stimulating hormone (TSH), left atrium (LA), left ventricular end diastolic diameter (LVD). CTRP6 concentrations were significantly lower in CAD compared with controls. The median and IQR CTRP6 of the subjects were 1.10 (0.76−1.82) in controls, 0.78 (0.60−1.43) in CAD, and 1.10 (0.76−1.76) in CAD+T2DM (P=0.001) (Figure 1).

Table 1 General Clinical and Laboratory Parameter in Participants

Variables	Controls	CAD	CAD and T2DM	*P* value
	(n=65)	(n=51)	(n=44)	
Men(n, %)	39(60)	46(90.20)	30(68.18)	0.001*
Age(years)#	60(55−69)	65(57−71)	64.5(55−73)	0.3876
BMI(kg/m^2)#	24.44(23.67−27.05)	24.89(23.14−27.1)	24.92(23.7−27.21)	0.9314
Gensini Score#	−	28(12−50)	19.5(11−39)	0.222
SBP(mmHg)&	135.98±18.6	137.24±19.96	133.82±18.41	0.825
DBP(mmHg)#	80(70−87)	78(70−86)	70(70−84)	0.1907
Smoking history(n, %)				0.078
Never	34	20	27	
Past smoking	7	5	7	
Current smoking	24	26	10	
Drinking history(n, %)				0.25
Never	42	29	34	
Past drinking	3	2	2	
Current drinking	20	20	8	
HT history(n, %)	25	34	29	
Stroke history(n, %)	1	1	2	
NE&	62.95±9.59	68.86±11.2	68.95±8.08	0.093
LY#	28.6(23.5−34.15)	21.25(16.6−30)	23.25(16.5−28.25)	0.0006*
HB&	140.63±17.32	143.06±14.81	136.39±18.31	0.332
PLT&	174.52±58.72	195.06±61.53	187±67.57	0.598
Glucose(mmol/L)#	5.38(5.12−5.82)	5.82(5.46−6.35)	7.82(6.59−9.15)	0.0001*
Albumin(g/L)#	42.8(40.7−45.3)	41.7(39−43.3)	42.1(38.5−45)	0.0529
TG(mmol/L)#	1.26(0.91−1.93)	1.37(0.93−1.82)	1.31(0.96−2.19)	0.8964
TC(mmol/L)#	4.41(3.74−4.89)	4.01(3.3−4.92)	3.71(3−4.81)	0.0455
ApoA(g/L)#	1.24(1.08−1.51)	1.08(0.97−1.23)	1.07(0.97−1.22)	0.0001*
ApoB(g/L)#	0.88(0.68−1.01)	0.83(0.64−1.05)	0.75(0.57−0.9)	0.0583
HDL-C(mmol/L)#	1.14(0.97−1.43)	0.97(0.85−1.1)	0.94(0.83−1.11)	0.0001*
LDL-C(mmol/L)&	2.49±0.78	2.5±0.83	2.21±0.92	0.464
Creatinine(μmol/L)#	63(55.5−74)	69.5(62−82)	66(54.5−77.5)	0.0659
BUN(mmol/l)#	5.58(4.74−6.55)	5.54(4.93−6.99)	6.15(4.75−7.3)	0.3410
UA(μmol/L)#	360.5(293.5−435)	368.5(308−448)	319(282.5−381)	0.0628

(Continued)

Table 1 (Continued).

Variables	Controls	CAD	CAD and T2DM	*P* value
	(n=65)	(n=51)	(n=44)	
Potassium(mmol/L)#	3.98(3.6−4.12)	4.01(3.78−4.29)	4.00(3.8−4.18)	0.3843
Calcium(mmol/L)#	2.26(2.2−2.38)	2.23(2.15−2.26)	2.27(2.18−2.33)	0.0214*
Phosphate(mmol/L)#	1.04(0.95−1.16)	0.965(0.91−1.07)	1.05(0.96−1.16)	0.0137*
FT3(pmol/L)#	4.97(4.39−5.64)	4.78(4.33−5.25)	4.74(4.16−5.53)	0.2836
FT4(pmol/L)#	10.93(9.35−11.74)	10.12(9.28−11.75)	11.56(10.77−13.31)	0.0031*
TSH(mIU/L)#	1.92(1.4−2.97)	1.69(1.26−2.96)	1.60(1.06−2.4)	0.2323
LA(mm)#	36(33−38)	37(35−38)	36(34−38)	0.2342
LVD(mm)#	48(45−51)	48(45−52)	48(44−51)	0.8025
EF(%)#	62(59−66)	60(56−62)	62(58−64.5)	0.0268*
CTRP6(ng/mL)#	1.10(0.76−1.82)	0.78(0.60−1.43)	1.10(0.76−1.76)	0.001*

Notes: &One–way ANOVA was performed. #Mann–Whitney *U*-test was performed. Chi-square test was performed to analyze categorical variables. *P value<0.05 was considered significant.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; NE, neutrophil; LY, lymphocyte; HB, hemoglobin; PLT, platelet; TG, triglyceride; TC, total cholesterol; Apo A, apolipoprotein A; Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, urea nitrogen; UA, uric acid; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; LA, Left atrium; LVD, left ventricular end diastolic diameter; EF, ejection fraction; CTRP6, C1q/TNF-related protein 6.

Association of CTRP6 with Other Factors

As shown in Table 2, Spearman correlation analysis was used to analyze the correlation between CTRP6 and other factors. In controls, CTRP6 levels were negatively correlated with LDL-C (ρ=−0.2769, P=0.028). In CAD group, CTRP6 levels were negatively correlated with ejection fraction (EF) (ρ=−03237, P=0.0342) and positively correlated with age (ρ=0.4121, P=0.0027), SBP (ρ=0.4012, P=0.0035), Creatinine (ρ=0.3295, P=0.0194), UA (ρ=0.3386, P=0.0162), and LVD (ρ=0.4277, P=0.0042). In CAD+T2DM group, CTRP6 levels were negatively associated with high-density lipoprotein cholesterol (HDL-C) (ρ=−0.3164, P=0.0387).

Serum CTRP6 and the Prevalence of CAD and T2DM in CAD Patients

Logistic regression models were performed to assess the association of CTRP6 levels with an increased risk of CAD. Model 1: crude OR, no risk factors were adjusted. Model 2: partially adjusted OR for risk factors including age and sex. Model 3: fully adjusted OR for risk factors. In model 3, multicollinearity was performed to assess the potential confounding covariates. As a common rule, a variance inflation factor (VIF) >5 was considered for the presence of multicollinearity. Therefore, these confounding factors did not enter the fully adjusted model. As shown in Table 3, serum CTRP6 levels were significantly related with CAD compared with controls in model 1 (P=0.01). This founding
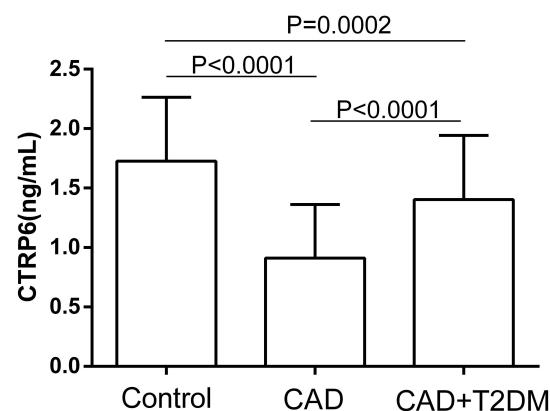

Figure 1 Comparison of serum CTRP6 among Control (n= 65), CAD (n= 51) and CAD+T2DM (n = 44). Mann–Whitney *U*-test was performed. P<0.05 means statistical significance.

Table 2 Bivariate Correlation Between Serum CTRP6 Levels and Other Variables

CTRP6	Control		CAD		CAD+T2DM	
	ρ	**P**	ρ	**P**	ρ	**P**
Age	0.1916	0.1264	0.4121	0.0027*	−0.1259	0.4154
BMI	0.1041	0.409	−0.2027	0.1536	0.051	0.7425
Gensini Score	−	−	0.0699	0.6262	0.0704	0.6499
SBP	0.0637	0.614	0.4012	0.0035*	0.0603	0.6973
DBP	−0.0628	0.6191	0.1061	0.4588	0.0148	0.9239
NE	0.1976	0.1175	0.1821	0.2057	−0.1116	0.4706
LY	−0.204	0.106	−0.1387	0.3366	0.1638	0.2881
HB	0.1768	0.1622	−0.2034	0.1566	0.1565	0.3104
PLT	−0.1203	0.3435	0.0908	0.5348	−0.2563	0.0931
Glucose(mmol/L)	0.1174	0.3637	0.0158	0.9163	0.1627	0.3032
Albumin(g/L)	0.0126	0.922	0.147	0.3241	0.0588	0.7079
TG(mmol/L)	−0.0637	0.6226	−0.2502	0.0899	0.1405	0.3629
TC(mmol/L)	−0.2146	0.0939	−0.0136	0.9278	0.0524	0.7357
ApoA(g/L)	0.0626	0.6259	0.036	0.8079	−0.2375	0.1252
ApoB(g/L)	−0.1589	0.2173	0.0512	0.7295	0.1757	0.2598
HDL-C(mmol/L)	0.0088	0.9457	0.0353	0.8119	−0.3164	0.0387*
LDL-C(mmol/L)	−0.2769	0.028*	−0.0377	0.7993	0.0488	0.7561
Creatinine(μmol/L)	0.1175	0.3549	0.3295	0.0194*	0.0252	0.8708
BUN(mmol/l)	−0.0948	0.456	0.2438	0.088	0.1893	0.2184
UA(μmol/L)	0.0696	0.585	0.3386	0.0162*	−0.023	0.8823
Potassium(mmol/L)	−0.0671	0.6011	0.0686	0.6359	0.1975	0.2042
Calcium(mmol/L)	0.0008	0.9948	0.0837	0.5633	0.1484	0.3364
Phosphate(mmol/L)	−0.0737	0.566	0.0952	0.5108	0.1945	0.2058
FT3(pmol/L)	−0.0601	0.6602	0.0164	0.9211	0.1691	0.3468
FT4(pmol/L)	−0.2355	0.0806	0.2683	0.0987	−0.0841	0.6418
TSH(mIU/L)	−0.0268	0.8444	−0.1827	0.2655	0.23	0.1978
LA(mm)	−0.062	0.6591	0.0555	0.7237	0.036	0.8347
LVD(mm)	−0.2129	0.1258	0.4277	0.0042*	−0.2631	0.121
EF(%)	−0.0585	0.6744	−0.3237	0.0342*	0.1022	0.5532

Notes: *P value<0.05 was considered significant. ρ means correlation coefficient.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NE, neutrophil; LY, lymphocyte; HB, hemoglobin; PLT, platelet; TG, triglyceride; TC, total cholesterol; Apo A, apolipoprotein A; Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, urea nitrogen; UA, uric acid; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; LA, Left atrium; LVD, left ventricular end diastolic diameter; EF, ejection fraction; CTRP6, C1q/TNF-related protein 6.

Table 3 Logistic Regression Analysis for the Serum CTRP6

(A)			
CAD compared with control			
Models	**OR**	**95% CI**	***P* values**
Model1	0.4507	0.2449–0.8292	0.01*
Model2	0.2934	0.1438–0.5989	0.001*
Model3	0.0329	0.0014–0.7789	0.034*
(B)			
CAD compared with CAD+T2DM			
Models	**OR**	**95% CI**	**P values**
Model1	1.9967	1.0545–3.7809	0.034*
Model2	2.212	1.1331–4.3181	0.02*
Model3	2.3748	1.1207–5.0323	0.024*

Notes: (**A**) Model 1: crude. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, body mass index, gensini score, diastolic blood pressure, hypertension history, stroke history, neutrophil, lymphocyte, hemoglobin, platelet, glucose, albumin, potassium, calcium, phosphate, thyroid stimulating hormone, left atrium. (**B**) Model 1: crude. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, gensini score, hypertension history, platelet, glucose, albumin, urea nitrogen, potassium, calcium, phosphate, free triiodothyronine, free thyroxine. *P value<0.05 was considered significant.
Abbreviations: OR, odds ratio; CI, confidence interval.

remained stable in model 2 (P=0.001) and model 3 (P=0.034). Relationship between CTRP6 and T2DM has been reported. Furthermore, we assessed the association of CTRP6 with an increased risk of T2DM in CAD patients. We found that CTRP6 levels were also related with T2DM in CAD patients (P=0.034). This founding remained stable after adjusting for age and sex (P=0.02) or other potential confounding covariates (P=0.024).

Discussion

In this study, we observed that circulating CTRP6 decreased significantly in CAD patients compared with controls. CTRP6 levels are higher in CAD+T2DM patients than in CAD patients. We found a negatively association between CTRP6 levels and the risk of CAD. Additionally, CTRP6 levels positively associated with the risk of T2DM in CAD patients. These results remained stable after adjustment for potential confounding factors. Collectively, these fundings suggested that CTRP6 related with CAD and T2DM.

CTRP family is a new family of secreted protein. It was first introduced by Lodish et al.[16] Previous studies revealed that CTRP family, including CTRP1-CTRP15, participated the process of metabolic and inflammatory pathways. For example, CTRP1 could decrease plaque formation and enhance insulin sensitivity, glucose and fatty acid oxidation.[17] Our previous study showed CTRP9 related with obesity.[18] Low circulating levels of CTRP3 have been associated with T2DM.[19] There are no studies concerning the association between CTRP6 and CAD. However, some studies showed that CTRP family played a pivotal role in regulation of cardiovascular diseases. The potential mechanism maybe due to that CTRP family regulates endothelial function, metabolic dysfunction, myocardial cell apoptosis, and so on. For example, CTRP2 was elevated in CAD patients. CTRP2 independently associated with the progression of CAD.[20] It was reported that CTRP3 was significantly inhibited in the presence with CAD.[21] Study showed that CTRP3 was downregulated in acute coronary syndrome patients and myocardial ischemia reperfusion (MI/R) mice. Liu[22] reported that CTRP6 may exert anti-atherosclerosis by inhibiting PDGF-BB-induced VSMC proliferation and migration through suppressing PI3K/Akt/mTOR signaling pathway. CTRP6 attenuates the progression of remodeling by inhibiting the proliferation and

migration of VSMCs. What is more, overexpression of CTRP3 ameliorated cardiac function and improved MI/R injury in mice.[23] Yi et al[24] reported that CTRP9 exerted anti-apoptotic function and reduced endoplasmic reticulum stress in MI/R injury. Moreover, CTRP9- knockout rats exhibited lower cardiac function and larger myocardial infarct size after MI/R injury.

However, the association between CTRP6 and CAD has not been described. CTRP6 is thought to be a new highly homologous family member of adiponectin paralogs. Adiponectin exerted anti-atherosclerotic, anti-diabetic, and anti-inflammatory activities in vivo.[25] Previous studies demonstrated that the CTRP6 acted an important role in insulin resistance, energy homeostasis and metabolism. It was showed that CTRP6 levels were higher in obese individuals than in healthy individuals. Multiple logistic regression analysis confirmed that circulating CTRP6 levels were significantly associated with obesity.[8] CTRP6 could inhibit the extracellular matrix deposition and promote AMPK pathway by promoting fatty acid oxidation in vivo and in vitro.[26] CTRP6 acted as an early responder to acute nutritional changes in adipose tissue. CTRP6-knockout mice exhibited increased adipogenic gene expression and whole-adipose tissue weight.[27] These results explained CTRP6 was higher in CAD with diabetes compared with that in CAD without diabetes. Since CAD is a disease characterized by abnormal lipid metabolism. Hence, we speculate that CTRP6 may be an important adipokine in the development of CAD.

The association between CTRP6 and T2DM had been described. Yang et al[14] found that circulating CTRP6 levels were higher in T2DM individuals than in healthy controls or impaired glucose tolerant patients. CTRP6 levels were positively correlated with BMI, Glucose, HbA1c, TC, and TG, whereas negatively associated with HDL-C. Multiple logistic regression models showed that CTRP6 concentrations were associated with developing T2DM after adjusting age and sex. The odds ratio (OR) and 95% confidence interval (CI) was 1.009 (1.006–1.011). Study founded that CTRP6 expression was significantly upregulated in obese and diabetic humans and mouse models. Insulin stimulated Akt phosphorylation was inhibited in mice treated with CTRP6. On the one hand, CTRP6-knockout mice exhibited improved insulin action and metabolic rate. On the other hand, overexpression of CTRP6 impaired glucose disposal in response to glucose and insulin challenge in mice.[28] In our study, we showed that CTRP6 was also related with T2DM in CAD patients.

Taken together, we assumed that this adipocytokine negatively related with CAD but positively associated with T2DM. However, there are still some limitations should be considered. Our study was a single-center cross-sectional study which limited the conclusion about the cause-and-effect relationship between circulating CTRP6 and CAD. Moreover, the sample size of our study was insufficient, and the result is limited. To validate these results, more patients should be recruited.

Conclusion

In conclusion, our study suggested that CTRP6 may reduce the incidence of CAD. Furthermore, CTRP6 levels may be a useful biomarker for predicting T2DM in CAD patients. Our study may serve as a basis for future studies to explore the potential preventive and therapeutic effects of CTRP6 on CAD and T2DM.

Ethics Statement

The study was approved by the Ethics Committee of Affiliated Aoyang Hospital of Jiangsu University. Each subject signed an informed consent. All human rights were observed in keeping with the Helsinki Declaration of 1975, as revised in 2008.

Funding

Disclosure

The authors report that they have no conflicts of interest in this work.

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