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Decreased serum levels of CTRP12/adipolin in patients with coronary artery disease in relation to inflammatory cytokines and insulin resistance

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ABSTRACT

Coronary artery disease (CAD) is the leading cause of death worldwide. Atherosclerosis as the main underlying mechanism of CAD is associated with inflammation and adipose tissue dysfunction. C1q/TNF-related protein12 (CTRP12) is a newly discovered adipokine which is a paralog of adiponectin. CTRP12 has anti-inflammatory and insulin sensitizing effects. Circulating levels of this adipokine have been reported to be lower in patients with type 2 diabetes and women with polycystic ovarian syndrome. The present study was undertaken for the first time to evaluate serum levels of CTRP12 in CAD patients and its association with anthropometric and biochemical parameters.

Serum levels of CTRP12 were measured using ELISA kit in 188 CAD patients (angiography confirmed) and 70 controls. The serum levels of adiponectin, TNF-α and IL-6 were measured using ELISA kits.

Serum levels of CTRP12 were found to be lower in CAD patients (585.48 ± 201.67 pg/mL) than in the controls (814.86 ± 247.85 pg/mL; $p < 0.001$). CTRP12 also showed an independent association with the risk of CAD (OR [CI] = 0.998 [0.996–0.999]; $p = 0.019$). Moreover, it showed an inverse correlation with HOMA-IR ($r = -0.298$; $p = 0.012$) and TNF-α ($r = -0.269$; $p = 0.023$) and a positive correlation with adiponectin ($r = 0.344$; $p = 0.003$) in the controls. In CAD patients, CTRP12 was inversely correlated with BMI ($r = -0.181$, $p = 0.013$), HOMA-IR (r = -0.199; $p = 0.006$), TNF-α (r = -0.259; $p < 0.001$) and IL-6 (r = -320; $p < 0.001$) and a positive correlation with high density lipoprotein-cholesterol($r = 0.342$; $p < 0.001$) and adiponectin ($r = 0.398$; $p < 0.001$).

The present study showed for the first time that serum levels of CTRP12 are independently associated with CAD and that CTRP12 is associated with several CAD risk factors. The results suggest a possible link between CTRP12 and pathogenic mechanisms of atherosclerosis, such as inflammation and high density lipoprotein-cholesterol metabolism; however, more study is required in this regard.

1. Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide [1]. Atherosclerosis, as the main underlying mechanism of CAD, has a close relation with obesity and inflammation [2,3]. Inflammation and dysregulation of lipoprotein metabolism increases foam cell and plaque formation on the arterial wall. Adipose tissue secrets adipokine, which effects whole body lipids, glucose metabolism and inflammation. Obesity and adipose tissue dysfunction leads to dysregulation of adipokine secretions, such as: adiponectin, resistin, visfatin, TNF-α and IL-6 [4]. Injection of IL-6 promotes atherosclerosis and TNF-α upregulates vascular adhesion molecules [5].

Adiponectin is an abundant adipokine which decreases in obesity [6]. Adiponectin exhibits anti-atherosclerotic activity such as a favorable effect on insulin sensitivity, lipid metabolism, inflammation and vascular function [6]. C1q/TNF-related protein (CTRP) is a newly

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discovered family of adipokines which are paralogs of adiponectin [7]. This family comprises 15 members (CTRP1 to CTRP15) [8]. CTRP12 (also known as adipolin) is a member of the CTRP family which is primarily secreted by adipose tissue with insulin sensitizing and anti-inflammatory effects [9]. CTRP12 exerts a positive effect on glucose and insulin metabolism by inhibiting gluconeogenesis and increasing glucose uptake in hepatocytes and adipocytes [9,10].

CTRP12 has been shown to decrease both expression of pro-inflammatory cytokines and macrophage accumulation in adipose tissue of obese mice [10]. There has been no data thus far regarding the association of CTRP12 and CAD. With regards to the effects of CTRP12 on inflammatory process and close relation of atherosclerosis with inflammation, the present study aimed to evaluate the serum levels of CTRP12 in CAD patients and its association with anthropometric, biochemical parameters and inflammatory cytokines.

2. Study population and methods

2.1. Study population

This case-control study was conducted on 188 CAD patients and 70 controls, aged between 45 and 75 years, who underwent angiography at Vliasr Hospital (Birjand, Iran), from Mar to Nov 2017. CAD was diagnosed by a cardiologist according to the angiography results and patients with > 50% stenosis in at least one coronary artery were categorized as CAD patients [11]. Subjects with < 30% stenosis in all coronary arteries were categorized as controls. In addition, subjects with unstable angina, carotid plaque or any history of cardiovascular disease, including cerebrovascular, peripheral artery and coronary artery disease and acute coronary syndrome were excluded from the control group. The exclusion criteria for the study population were as follows: diabetes mellitus, myocardial infraction, stroke, autoimmune disease, chronic inflammation, kidney disease, cancer and treatment with thiazolidinedione family drugs. Subjects who had smoked within the last three months were considered to be smokers. The study was carried out in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Birjand University of Medical Sciences. All study participants signed written consent forms.

2.2. Anthropometric and laboratory measurements

The body mass index (BMI) was calculated using the standard formula (weight (kg)/height (m^2)). A standard sphygmomanometer was used to measure the systolic blood pressure and diastolic blood pressure in a sitting position after 15 min of rest. Venous blood was collected after overnight fasting. The fasting blood glucose, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, total cholesterol, triglycerides, alanine amino transferease, aspartate amino transferease and creatinine were measured by auto analyzer using commercially available kits (Pars Azmoon; Iran). Fasting insulin levels were measured by an ELISA kit (Monobind; USA). The standard formula ([fasting blood glucose (mg/dl)] × [fasting blood insulin (μU/mL)/405]) was used to calculate the homeostasis model assessment of insulin resistance (HOMA-IR) [12].

2.3. Measuring cytokine and adipokine levels

ELISA kits were used to assess the levels of TNF-α (R & D Systems; USA; Cat# DTA00C) and inteleukin-6 (IL-6; R & D Systems; USA; Cat# HS600B). Minimum detectable range for TNF-α and IL-6 were 0.5 pg/mL and 0.11 pg/mL, respectively. Furthermore, intra- and inter-assay coefficients of variation (CV) of TNF-α and IL-6 were 5.2 and 7.4, and 6.9 and 9.6, respectively. Serum levels of adiponectin were measured using an ELISA kit (Adipogen; South Korea; Cat# AG-45A-0001YEK-KI01) with minimum detectable range of 0.1 pg/mL and intra- and inter-assay CV of 3.4% and 4.3%, respectively. Also, an ELISA kit was used to measure CTRP12 (Aviscera Bioscience; USA; Cat# SK00392-06) with detection limit of 10 pg/mL and intra- and inter-assay CV of 7% and 6%, respectively.

2.4. Statistical analysis

Categorical data was tested using the chi-square test and is presented as frequency and percentage. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Variables with a normal distribution were tested between groups using the student *t*-test and are shown as mean ± standard deviation (SD). Non-normal distributed variables were tested using the Mann-Whitney *U* test and were recorded as median and interquartile range (IQR). Analysis of covariance (ANCOVA) was performed to remove any possible effect of covariates on circulating levels of CTRP12. Binary logistic regression was carried out to assess the risk of CAD in relation to serum levels of CTRP12. Correlation analysis was performed to assess the correlation of CTRP and anthropometric and biochemical variables. The non-normal distributed data was logarithmically transformed before correlation and regression analysis. In addition, multivariate linear regression was carried out with CTRP12 as the dependent variable and all variables correlated with CTRP12 as independent variables. The receiver operating curves (ROC) were plotted to assess the ability of CTRP12 to discriminate the CAD and control group. All statistical analysis were conducted with SPSS 16 (SPSS, IL, USA) and p value < 0.05 considered as statistical significant.

3. Results

3.1. Anthropometric and biochemical measurements

There were no significant difference in terms of age (p = 0.213), sex (p = 0.831), BMI (p = 0.125) and fasting blood glucose (p = 0.125) between the CAD patients and controls. Likewise, systolic blood pressure (p = 0.089) and diastolic blood pressure (p = 0.088) showed no significant difference between groups. CAD patients demonstrated higher levels of insulin (p = 0.004) and HOMA-IR (p < 0.001) compared to controls. Moreover, triglycerides (p = 0.001), total cholesterol (p = 0.010) and low density lipoprotein-cholesterol (p = 0.032) levels were higher in the CAD group than in the controls and high density lipoprotein-cholesterol (p = 0.029) was lower. Aspartate amino transferease, alanine amino transferease and creatinine showed no significant differences between groups. Furthermore, a higher number of subjects used statins and hypertensive medication and were smokers in the CAD group than in the control group (p < 0.001). Table 1 lists the anthropometric and biochemical measurements.

3.2. Serum levels of cytokine and adipokine

Serum levels of TNF-α were found to be higher in CAD patients (27.89 ± 7.16 pg/mL) than in the controls (21.39 ± 7.85 pg/mL; p < 0.001; Fig. 1a). Likewise, serum levels of IL-6 showed higher levels in the CAD group (8.67 ± 3.66 pg/mL) compared to the control group (5.39 ± 1.82 pg/mL; p < 0.001; Fig. 1b). However, serum levels of adiponectin showed lower levels in CAD patients (8.72 ± 3.02 μg/mL) when compared with the controls (11.46 ± 3.82 μg/mL; p < 0.001; Fig. 1c). Moreover, CTRP12 serum levels were found to be lower in CAD patients (585.48 ± 201.67 pg/mL) than in the controls (814.86 ± 247.85 pg/mL; p < 0.001; Fig. 2a).

ANCOVA was performed to remove the effect of covariates (age, sex, BMI, HOMA-IR, adiponectin and medication). The results showed that the decrease in the levels of CTRP12 (608.99 ± 172.83 vs. 749.11 ± 200.62 pg/mL) were independent of the covariates (p < 0.001). Serum levels of CTRP12 were found to be higher in women (761.0 ± 252.84 pg/mL) than in men (595.63 ± 212.82 pg/

Table 1
Clinical and biochemical characteristics of study population.

Variables	Non-CAD	CAD	p value
Gender [male (%)]	48 (67.6)	129 (69)	0.831
Age (year)	56.70 ± 8.65	58.18 ± 7.82	0.213
BMI (kg/m^2)	25.41 ± 3.27	26.19 ± 3.78	0.125
Systolic blood pressure (mm Hg)	130 (118–140)	130 (120–145)	0.089
Diastolic blood pressure (mm Hg)	80 (74–90)	80 (74–90)	0.088
Fasting blood glucose (mg/dl)	93.08 ± 10.93	95.38 ± 10.60	0.125
HOMA-IR	0.85 ± 0.51	1.20 ± 0.79	0.001
Insulin (uU/mL)	3.2 (2.1–5.4)	4.7 (2.1–7.6)	0.004
Triglycerides (mg/dL)	121.46 ± 46.22	146.50 ± 53.31	0.001
Total cholesterol (mg/dL)	170.44 ± 38.37	185.00 ± 47.66	0.010
Low density lipoprotein-cholesterol (mg/dL)	103.06 ± 32.11	113.29 ± 35.01	0.032
High density lipoprotein–cholesterol (mg/dL)	46.02 ± 6.97	43.65 ± 9.71	0.029
Creatinine (mg/dL)	1.13 ± 0.18	1.17 ± 0.18	0.197
Aspartate amino transferease (U/L)	17.1 (14–22)	19 (16–25)	0.201
Alanine amino transferease (U/L)	18.04 ± 7.54	20.53 ± 8.2	0.194
Statin use [n (%)]	23 (32.4)	107 (57.2)	< 0.001
Antihypertensive medication [n (%)]	11 (15.5)	70 (37.4)	0.001
Smoker [n (%)]	8 (11.3)	79 (42.2)	< 0.001

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance.

mL; $p < 0.001$; Fig. 2b). CTRP12 was compared between patients according to the number of vessels with > 50% stenosis and the results showed no significant difference.

3.3. Association of CTRP12 with anthropometric and biochemical parameters

Correlation analysis was performed on the control and CAD groups. In the control group, correlation analysis showed a negative correlation of CTRP12 with BMI ($r = -0.259$; $p = 0.029$), insulin ($r = -0.295$; $p = 0.012$), HOMA-IR ($r = -0.298$; $p = 0.012$) and TNF-α ($r = -0.269$; $p = 0.023$) and a positive correlation with high density lipoprotein-cholesterol ($r = 0.301$; $p = 0.011$) and adiponectin ($r = 0.344$; $p = 0.003$; Table 2). Significant correlations were adjusted for adiponectin serum level. The results showed that all correlations remained significant except the correlation of CTRP12 with BMI (Table 2). In addition, multivariate linear regression showed that CTRP12 was independently associated with HOMA-IR, TNF-α and adiponectin (Table 2).

Correlation analysis in CAD patients showed a negative correlation of CTRP12 with BMI ($r = -0.181$, $p = 0.013$), insulin ($r = -0.187$; $p = 0.010$), HOMA-IR ($r = -0.199$; $p = 0.006$), TNF-α ($r = -0.259$; $p < 0.001$) and IL-6 ($r = -0.320$; $p < 0.001$) and a positive correlation with high density lipoprotein-cholesterol ($r = 0.342$; $p < 0.001$) and adiponectin ($r = 0.398$; $p < 0.001$) (Table 3). Furthermore, after adjusting for adiponectin all correlation remained significant (Table 3). Also, multivariate linear regression demonstrated an independent association of CTRP12 with BMI, HOMA-IR, TNF-α, IL-6, high density lipoprotein-cholesterol and adiponectin (Table 3).

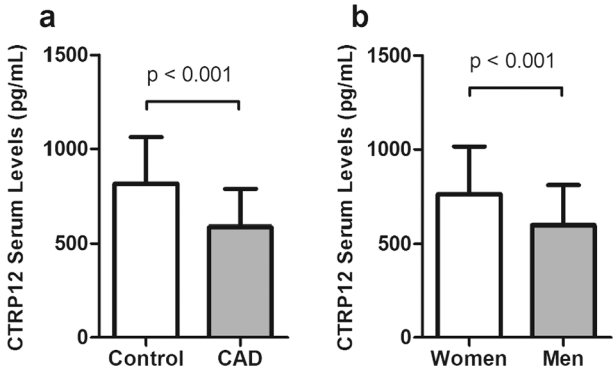

Fig. 2. Serum levels of CTRP12 in study population. (a) Serum levels of CTRP12 were found to be lower in CAD patients compared to controls ($p < 0.001$). (b) Serum levels of CTRP12 were higher in women compared with men ($p < 0.001$).

3.4. Association of CTRP12 with CAD

Logistic regression was carried out to evaluate the association of CTRP12 serum level with the risk of CAD and the results are given in Table 4. In the crude model, CTRP12 was found to be associated with CAD (OR [CI] = 0.995 [0.994–0.997]; $p < 0.001$). In the next model, CTRP12 was significantly associated with the risk of CAD after adjusting for the effects of age, sex and BMI (OR [CI] = 0.995 [0.993–0.996]; $p < 0.001$). After adjusting for the effect of other possible covariates, the results showed an independent association of CTRP12 with the risk of CAD (OR [CI] = 0.998 [0.996–0.999]; $p = 0.019$). However, CTRP12 showed no association with CAD severity as defined by the number of vessels with > 50% stenosis.

ROC analysis was performed to evaluate the ability of CTRP12 to differentiate between the CAD and control groups. The results showed a cut-off value of CTRP12 < 645.5 pg/mL had good sensitivity (0.746) and specificity (0.61) for differentiating between the CAD and control groups (area under curve [CI] = 0.76 [0.695–0.826]; $p < 0.001$; Fig. 3).

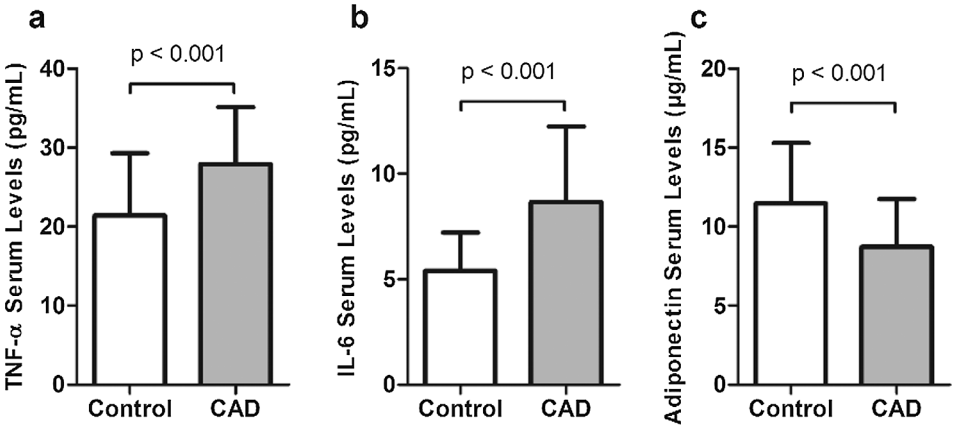

Fig. 1. Serum levels of TNF-α, IL-6 and adiponectin in CAD patients and controls. (a) Serum levels of TNF- α showed a higher levels in CAD patients compared to controls ($p < 0.001$). (b) IL-6 serum levels were found to be higher in CAD patients compared to controls ($p < 0.001$). Serum levels of adiponectin showed lower levels in CAD patients compared with controls ($p < 0.001$).

Table 2
Association of CTRP12 with anthropometric and metabolic parameters in controls.

Variables	Unadjusted Pearson coefficient	Adjusted for adiponectin Pearson coefficient	Multiple linear regression B (standard error)
Age	0.035		
BMI	−0.259*	−0.200	−15.01 (8.12)
Systolic blood pressure[a]	−0.115		
Diastolic blood pressure[a]	−0.042		
Fasting blood glucose	0.021		
Insulin[a]	−0.295*	−0.342**	
HOMA-IR	−0.298*	−0.317**	−114.44(50.87)*
Triglycerides	−0.189		
Total cholesterol	0.009		
low density lipoprotein-cholesterol	0.168		
High density lipoprotein-cholesterol	0.301*	0.283*	6.79 (3.75)
Creatinine	0.121		
Aspartate amino transferease[a]	−0.172		
Alanine amino transferease	−0.173		
TNF-α[a]	−0.269*	−0.238*	−396.80 (149.57)*
IL-6[a]	−0.201		
Adiponectin	0.344**		15.65 (6.87)*

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; ; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.
* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
[a] Logarithmic transformation was performed.

Table 4
Odds ratios of CAD presence according to CTRP12 serum levels.

Model	Odd ratio (95% confidence interval)	p
Crude model	0.995 (0.994–0.997)	< 0.001
Adjusted model*	0.995 (0.993–0.996)	0.019

* Adjusted for age, sex and BMI.

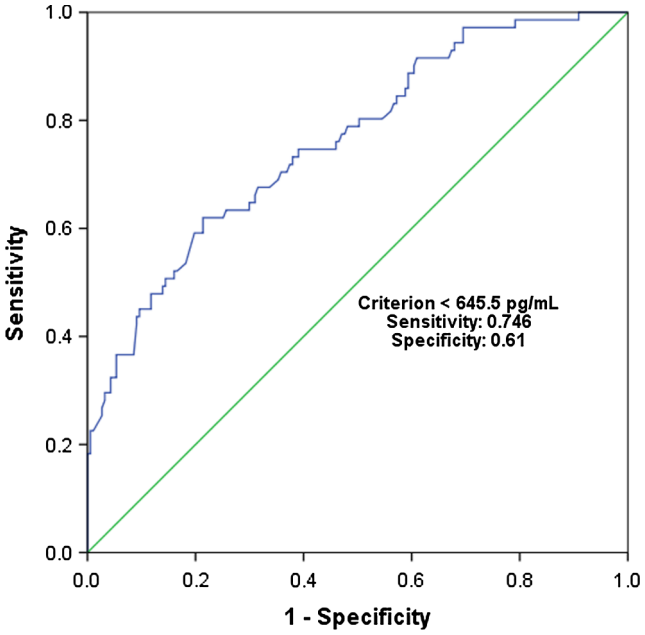

Fig. 3. ROC curve for CTRP12. A CTRP12 < 645.5 pg/mL (area under curve [CI] = 0.76 [0.695–0.826]; p < 0.001) was the cut-off values to distinguish between CAD and controls.

4. Discussion

This is the first study to report an association between CTRP12 and CAD. The main findings of the present study are that a decrease in CTRP12 levels in CAD patients is associated with the levels of BMI, insulin resistance, inflammatory cytokines and adiponectin.

Previous studies have shown perturbation in the circulating levels of CTRP family members in the context of metabolic diseases such as non-alcoholic fatty liver, metabolic syndrome, diabetes and CAD [13–19]. Several studies have reported on the relation of CTRP12 with glucose and insulin metabolism parameters [9,17,20,21]. In addition, circulating levels of CTRP12 have been shown to be lower in type 2 diabetic patients and insulin resistance in PCOS patients [17,20]. In the present

Table 3
Association of CTRP12 with anthropometric and metabolic parameters in CAD.

Variables	Unadjusted Pearson coefficient	Adjusted for adiponectin Pearson coefficient	Multiple linear regression B (standard error)
Age	−0.006		
BMI	−0.181*	−0.159*	−7.592 (3.18)*
Systolic blood pressure [a]	0.009		
Diastolic blood pressure[a]	−0.100		
Fasting blood glucose	−0.061		
Insulin[a]	−0.187*	−0.247**	
HOMA-IR	−0.199**	−0.261**	−54.70 (15.27)**
Triglycerides	0.075		
Total cholesterol	0.122		
low density lipoprotein-cholesterol	0.080		
High density lipoprotein-cholesterol	0.342**	0.297**	5.09 (1.27)**
Creatinine	−0.032		
Aspartate amino transferease[a]	−0.086		
Alanine amino transferease	0.008		
TNF-α[a]	−0.259**	−0.237**	−242.77 (109.19)*
IL-6[a]	−0.320**	−0.280**	−174.87 (72.52)*
Adiponectin	0.398**		21.26 (4.12)**

BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6.
* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
[a] Logarithmic transformation was performed.

study, serum levels of CTRP12 were found to be lower in CAD patients. With regard to the close association of CTRP12 with insulin resistance and the difference in HOMA-IR levels in the study groups, the present study adjusted for the effect of HOMA-IR and other covariates on serum levels of CTRP12. The results showed that a decrease in serum CTRP12 was independent of the levels of HOMA-IR and other covariates. Furthermore, a lower CTRP12 level was independently associated with the risk of CAD.

There are no reports regarding the association of CTRP12 and CAD in previous studies; however, several members of the CTRP family have been reported to be associated with CAD, such as CTRP1, CTRP3, CTRP9 and CTRP13 [13,22,23]. Also, several possible mechanisms link this family of adipokines to atherosclerosis, such as suppression of inflammation, endothelial dysfunction and lipid metabolism [8,19]. This is the first report addressing the association of CTRP12 and CAD, but the mechanism linking low CTRP12 to CAD as yet is not clear. Further study is needed to dissect possible mechanisms. Also, CTRP12 was found to be higher in women than in men. This result is in line with those of previous studies that reported a sexually dimorphic pattern of circulating levels of CTRP family members [8,19].

It has also been reported that CTRP12 decreased after a 2-hour oral glucose tolerance test (OGTT) [17]. Metformin therapy has been found to increase circulating CTRP12 and several studies have reported an inverse association of CTRP12 with the parameters of insulin and glucose metabolism [17,24]. In the present study, CTRP12 was found to be inversely associated with HOMA-IR. Wei et al. [25] showed that CTRP12 promotes glucose uptake and suppresses gluconeogenesis by activating the PI3K-Akt signaling pathway and improving insulin sensitivity. The results of the present study provide further *in vivo* evidence for the association of CTRP12 with insulin metabolism.

A previous study has reported that *Ctrp12* (+/−) mice have shown alternations in their lipid and cholesterol metabolism [26]. Tan et al. showed that partial *Ctrp12* deficient mice exhibit lower hepatic triglycerides –very low density lipoprotein secretions. The present study demonstrated no association between CTRP12 and low density lipoprotein-cholesterol, total cholesterol or TG [26]. This contradiction could be the result of the difference between the nature of human and animal studies. However, the current results indicate a positive association of CTRP12 with high density lipoprotein-cholesterol. This result requires further study to determine a possible causal relationship between CTRP12 and high density lipoprotein-cholesterol metabolism.

Enomoto et al. [10] showed that adenovirus-mediated upregulation of CTRP12 decreased macrophages recumbent in adipose tissue and suppressed expression of inflammatory cytokines (TNF-α, Il-1β and MCP-1) in adipose tissue. Also, the CTRP12 dose dependently attenuated LPS-mediated upregulation of TNF-α, IL-1β and MCP-1 in macrophages and TNF-α suppressed CTRP12 expression by adipocytes [10]. Previous studies have shown an inverse correlation between CTRP12 and C-reactive protein (CRP) as an inflammatory marker [24]. The results of the present study showed an inverse correlation of CTRP12 with inflammatory cytokines (IL-6 and TNF-α), especially in CAD patients. This is the first *in vivo* report on the relation of CTRP12 with inflammatory cytokines. CTRP12 also was found to be lower in the adipose tissue of obese mice and several studies have reported an inverse correlation of BMI with CTRP12 [25]. In line with the results of previous studies [10,24,25], the current results showed an inverse association of CTRP12 with BMI. The inverse relation of CTRP12 with BMI and inflammatory cytokines suggests a possible negative effect of the inflammatory milieu in decreasing the level of CTRP12, as previously reported in animal models [10].

In conclusion, the present study reports an independent association of CTRP12 with CAD for the first time. These results indicate a relationship between CTRP12 and BMI, inflammatory cytokines, insulin resistance, high density lipoprotein-cholesterol and adiponectin. This result suggests the possible link of CTRP12 with pathogenic mechanisms of atherosclerosis, such as inflammation and high density lipoprotein-cholesterol metabolism. A causal relation between CTRP12 and CAD could not be concluded from the present study results, but its association with the risk factors of CAD suggest a link between a decrease in CTRP12 and the pathogenesis of CAD. Further study is required in this regard.

Conflict of interest

Authors declare no conflict of interest.

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