Predictive value of serum CTRP9 and STIM1 for restenosis after cerebrovascular stent implantation and its relationship with vasoactive substances and inflammatory cytokines

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Abstract. Predictive value of serum complement Clq tumor necrosis factor-related protein 9 (CTRP9) and serum stromal interaction molecule 1 (STIM1) was investigated for restenosis after cerebrovascular stent implantation, as well as its relationship with vasoactive substances and inflammatory cytokines. In this prospective study, 128 patients with cerebral infarction treated with cerebrovascular stent implantation in Yantaishan Hospital were recruited. A total of 66 cases with restenosis after cerebrovascular stent implantation were included in group A, and 62 cases without stenosis were included in group B. Serum CTRP9 and STIM1 levels were measured by enzyme-linked immunosorbent assay (ELISA). ROC curves of serum CTRP9 and STIM1 levels in patients with postoperative restenosis were drawn. The vasoactive substances nitric oxide (NO), tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) were analyzed by ELISA. The correlation of serum CTRP9, STIM1 levels and NO, TNF-α, IL-6 were analyzed by Pearson correlation coefficient. Serum CTRP9 and NO levels in group A were significantly lower than those in group B. The levels of serum STIM1, TNF-α and IL-6 in group A were significantly higher than those in group B ($P<0.001$). The sensitivity and specificity of serum CTRP9 level in the diagnosis of restenosis after cerebrovascular stent implantation were, respectively, 59.68 and 75.76%. Those of serum STIM1 were, respectively, 87.10 and 46.97% and those of the combination of serum CTRP9 and STIM1 were 90.32 and 48.48%. Serum CTRP9 level was positively correlated with NO, and negatively correlated with TNF-α and IL-6. STIM1 was positively correlated with TNF-α and IL-6, and negatively correlated with NO ($P<0.001$). Serum CTRP9 level was significantly decreased in patients with restenosis after cerebrovascular stent implantation, while STIM1 level was significantly up-regulated. Both were correlated with the change of NO, IL-6 and TNF-α levels, therefore they could be used as biological indicators for prediction of restenosis after cerebrovascular stent implantation.

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Introduction

With the change in people's quality of life, the incidence of cerebral infarction increases, leading to an increase of mortality in patients with cardiovascular and cerebrovascular diseases (1). For stroke patients, conventional treatment mainly includes anticoagulation, thrombolysis and other supportive treatments (2). In recent years, cerebrovascular stent implantation has been applied in the interventional therapy of cerebral infarction, which has achieved great success and has been widely applied in clinical practice (3). However, cerebrovascular restenosis is often complicated during the later operation of stent implantation, which is one of the difficulties that hinder the recovery of patients after surgery. The disease deteriorates severely, and the mortality is high (4,5). Therefore, it is urgent to study predictors of restenosis after cerebrovascular stent implantation to save patients' lives and assist their recovery.

It has been found that serum complement Clq tumor necrosis factor-related protein 9 (CTRP9) is one of the adipocyte factors synthesized and released by adipose tissue. It is highly homologous with adiponectin during evolution, has the functions of regulating inflammatory response, anti-endothelial dysfunction, protecting myocardium and the metabolism of lipolysaccharide, and plays a role in regulating the stability of the body (6-10). Stromal interaction molecule 1 (STIM1) is closely related to endothelial cell function and homing of endothelial progenitor cells. The increased content may lead to injury of endothelial cells and delay of stent reendothelialization after cardiac stent implantation (11,12). However, there are relatively few studies on the effect of serum CTRP9 and STIM1 on restenosis after cerebrovascular stent implantation. Therefore, this study investigated the predictive value of serum CTRP9 and STIM1 for restenosis after cerebrovascular stent implantation, and their relationship with the vasoactive substances nitric oxide (NO), tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6) to validate biological indicators of early restenosis in cerebrovascular stent implantation.

Table I. Baseline data of patients.

Characteristics	Group A (n=66)	Group B (n=62)	χ^2 test	P-value
Age (years)	53.58±7.36	54.36±7.86	0.580	0.563
Sex [n (%)]			0.058	0.809
Male	38 (57.58)	37 (59.68)		
Female	28 (42.42)	25 (40.32)		
Height (cm)	163.53±7.45	164.35±7.14	0.635	0.527
BMI (kg/m^2)	25.64±2.34	25.57±2.28	0.171	0.864
Smoking history [n (%)]	48 (72.73)	44 (70.97)	0.049	0.825
Drinking history [n (%)]	51 (77.27)	49 (79.03)	0.058	0.810
Past history [n (%)]				
Hypertension	25 (37.88)	22 (35.48)	0.079	0.779
Coronary heart disease	14 (21.21)	11 (17.74)	0.245	0.621
Diabetes mellitus	17 (25.76)	15 (24.19)	0.042	0.838
Hyperlipidemia	16 (24.24)	17 (27.42)	0.169	0.681

Patients and methods

Baseline data. In this prospective study, 128 cases of cerebral infarction treated with cerebrovascular stent implantation in Yantaishan Hospital (Yantai, China) from March 2013 to January 2016 were selected as experimental subjects. A total of 66 cases with restenosis after cerebrovascular stent implantation were included in group A, while 62 cases without stenosis were included in group B. There were 75 males and 53 females, with an average age of 54.82±7.74. There was no significant difference in gender, age, etc. between the two groups (all P>0.05; Table I).

Inclusion and exclusion criteria. Inclusion criteria: Patients diagnosed with cerebral infarction by cerebral angiography technology.

Exclusion criteria: Patients with abnormal function of previous coagulation; patients with contraindications of stent implantation; patients complicated with endocrine system diseases; patients with severe hepatic and kidney function obstacle; patients with cognitive impairment or communication barrier; patients with poor compliance.

This study was approved by the Ethics Committee of Yantaishan Hospital (approval no. YTSH20130301). All the patients and their families were well informed, and a signed informed consent was obtained.

Experimental reagents and materials. CTRP9 kit was purchased from Aviscera Bioscience Co., (XY-RD191180200R). STIM1 kit was purchased from Shanghai Renjie Biotechnology Co., Ltd. (RJ12740). NO kit and IL-6 kit were purchased from Wuhan Mskbio Biotechnology Co., Ltd. (KT76381, KT63251). TNF-α kit was purchased from Nanjing Camilo Bioengineering Co., Ltd. (H-KMLJ37541).

Detection of serum CTRP9 and STIM1. Serum expression levels of CTRP9 and STIM1 of study subjects were measured by ELISA. After 1 month of cerebrovascular stent implantation, 5 ml of patient's venous blood was collected and centrifuged at room temperature for 8 min. The serum was separated at 1,500 x g, sealed and stored at -80˚C for testing. A total of 100 μl of serum sample was added to the orifice coated with anti-CTRP9 antibody. A blank well and a standard well were set up. The CTRP9 antibody was added at 37˚C for reaction for 90 min, and the liquid was discarded, then dried and washed repeatedly three times. A total of 150 μl of the chromogenic reagent was added at 37˚C for reaction for 30 min. A total of 50 μl of the mixture was taken out, mixed and put into enzyme-labelling measuring instrument to measure the average optical density of each well by 500 nm wavelength. STIM1, NO, TNF-α and IL-6 levels were detected as above in strict accordance with the ELISA kit instructions.

Observation indexes. Comparison of serum CTRP9 and STIM1 levels of patients in the two groups; comparison of NO, TNF-α and IL-6 levels of patients in the two groups; comparison of diagnostic efficacy of serum CTRP9, STIM1 and their combination; analysis of the correlation between serum CTRP9, STIM1 levels and NO, TNF-α, IL-6 levels.

Statistical methods. SPSS 19.0 statistical software (Shanghai Kabei Information Technology Co., Ltd.) was used for statistical analysis of experimental data. The counting data were tested by chi-square test. Measurement data were expressed as mean ± standard deviation. T test was used for comparison between two groups. The diagnostic value of CTRP9, STIM1 and their combination in restenosis after cerebrovascular stent implantation was analyzed by ROC. Correlation analysis was performed by Pearson's correlation coefficient. Graphpad Prism8 was used for image rendering. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of serum CTRP9 and STIM1 levels of patients in the two groups. Serum CTRP9 level in group A was

Table II. Comparison of serum CTRP9 and STIM1 levels in the two groups.

Factors	Group A (n=66)	Group B (n=62)	t	P-value
CTRP9 (ng/ml)	159.64±32.55	184.53±34.53	4.190	<0.001
STIM1 (U/l)	12.15±1.44	11.31±0.92	3.905	<0.001

Table III. Comparison of NO, TNF-α, IL-6 levels of patients in the two groups.

Factors	Group A (n=66)	Group B (n=62)	t	P-value
NO (mol/l)	156.57±12.58	172.73±13.83	6.901	<0.001
TNF-α (ng/l)	10.52±1.68	7.78±0.93	11.310	<0.001
IL-6 (ng/l)	98.75±13.53	83.48±9.84	7.263	<0.001

NO, nitric oxide; TNF-α, tumor necrosis factor α; IL-6; interleukin-6.

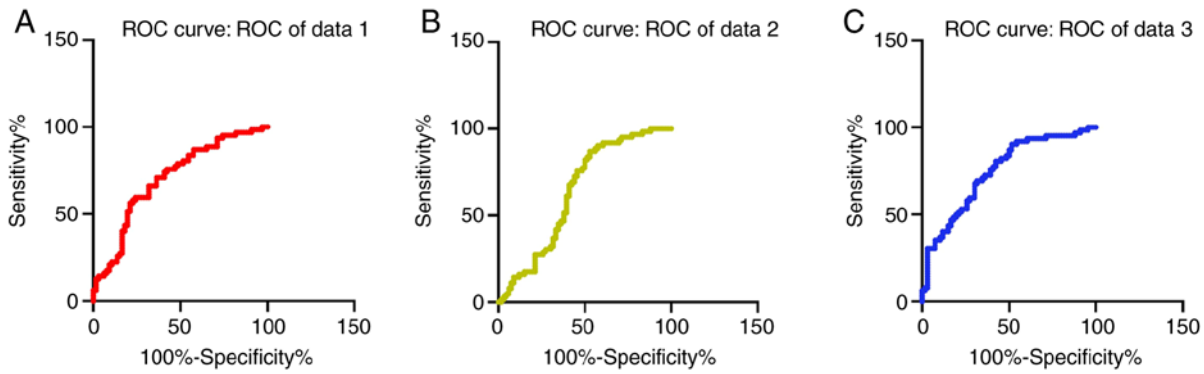

Figure 1. Analysis of serum CTRP9 level in the diagnostic efficacy of restenosis after cerebrovascular stent implantation. (A) ROC curve analysis showed that the sensitivity of serum CTRP9 level in the diagnosis of restenosis after cerebrovascular stent implantation was 59.68%, the specificity was 75.76%, AUC was 0.705 and cut off was 180.6. (B) ROC curve analysis showed that the sensitivity of serum STIM1 level in diagnosis of restenosis after cerebrovascular stent implantation was 87.10%, the specificity was 46.97%, AUC was 0.637 and cut off was 12.24. (C) The pre-1 fitting of probability value in Logistics regression model combined ROC curve results showed that the sensitivity of serum CTRP9 and STIM1 levels in the combined diagnosis of restenosis after cerebrovascular stent implantation was 90.32%, the specificity was 48.48%, AUC was 0.747 and cut off was 0.484.

significantly lower than that in group B. Serum STIM1 level in group A was significantly higher than that in group B. The differences were statistically significant (both P<0.001). More details are shown in Table II.

Comparison of NO, TNF-α, IL-6 levels of patients in the two groups. Serum NO level in group A was significantly lower than that in group B. Serum TNF-α and IL-6 levels in group A were significantly higher than those in group B. The differences were statistically significant (all P<0.001). More details are shown in Table III.

Comparison of serum CTRP9, STIM1 levels and combined diagnostic efficacy by ROC curve analysis. The sensitivity, specificity, AUC and cut-off of serum CTRP9 level in the diagnosis of restenosis after cerebrovascular stent implantation were 59.68, 75.76, 0.705 and 180.6%, respectively. The sensitivity, specificity, AUC and cut-off of serum STIM1 level in diagnosis of restenosis after cerebrovascular stent implantation were 87.10, 46.97, 0.637 and 12.24%, respectively. The sensitivity, specificity, AUC and cut-off of the combination of serum CTRP9 and STIM1 levels in the combined diagnosis of restenosis after cerebrovascular stent implantation were 90.32, 48.48, 0.747 and 0.484%, respectively (Fig. 1).

Analysis of the correlation between serum CTRP9, STIM1 levels and NO, TNF-α, IL-6 levels. After cerebrovascular stent implantation, the level of CTRP9 was positively correlated with NO (r=0.711, P<0.001), and negatively correlated with TNF-α (r=-0.761, P<0.001) and IL-6 (r=-0.751, P<0.001). The level of STIM1 was negatively correlated with NO (r=-0.761, P<0.001), and positively correlated with TNF-α (r=0.776, P<0.001) and IL-6 (r=0.709, P<0.001) (Fig. 2).

Discussion

Many studies have shown that the incidence of postoperative in-stent restenosis is higher than that of non-operative surgery (13,14). However, the mechanism of restenosis after cerebrovascular stent implantation remain unclear. Most

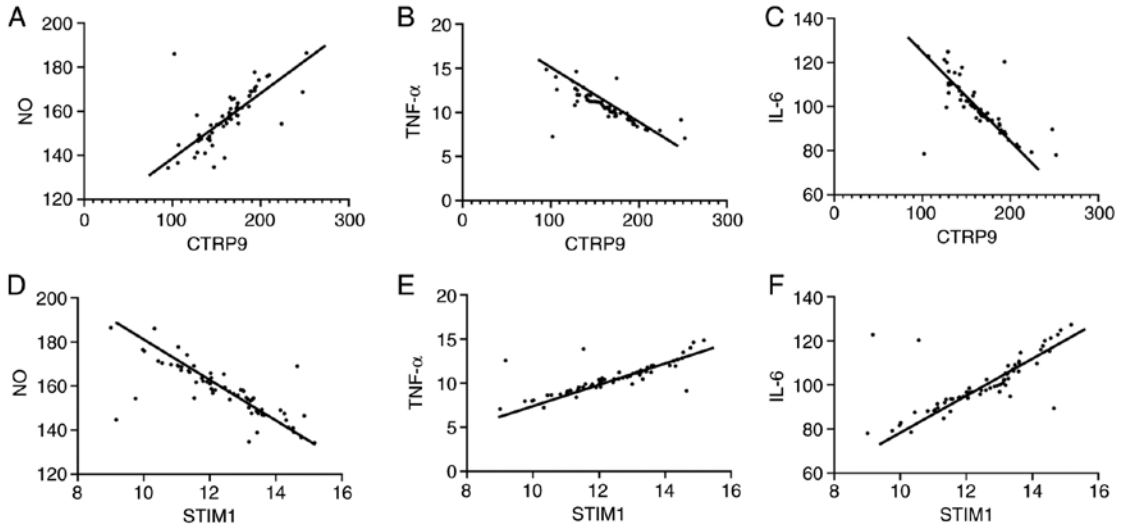

Figure 2. Analysis of the correlation between serum CTRP9, STIM1 levels and NO, TNF-α, IL-6 levels after cerebrovascular stent implantation. (A) Analysis of the correlation between serum CTRP9 levels and NO levels after cerebrovascular stent implantation. Pearson's analysis showed that the expression of CTRP9 and NO was positively correlated (r=0.711, P<0.001). (B) Analysis of the correlation between serum CTRP9 levels and TNF-α levels after cerebrovascular stent implantation. Pearson analysis showed that the expression of CTRP9 and TNF-α was negatively correlated (r=-0.761, P<0.001). (C) Analysis of the correlation between serum CTRP9 levels and IL-6 levels after cerebrovascular stent implantation. Pearson's analysis showed that the expression of CTRP9 and IL-6 was negatively correlated (r=-0.751, P<0.001). (D) Analysis of the correlation between serum STIM1 levels and NO levels after cerebrovascular stent implantation. Pearson's analysis showed that the expression of STIM1 and NO was negatively correlated (r=-0.761, P<0.001). (E) Analysis of the correlation between serum STIM1 levels and TNF-α levels after cerebrovascular stent implantation. Pearson's analysis showed that the expression of STIM1 and TNF-α was positively correlated (r=0.776, P<0.001). (F) Analysis of the correlation between serum STIM1 levels and IL-6 levels after cerebrovascular stent implantation. Pearson's analysis showed that the expression of STIM1 and IL-6 was positively correlated (r=0.709, P<0.001). NO, nitric oxide; TNF-α, tumor necrosis factor α; IL-6; interleukin-6.

scholars agree that it is related to vascular remodeling, intima abnormal growth, polymer absorption hindering inflammatory response and postoperative vascular elastic retraction and other factors (15,16). It is of practical significance to find out the cause of restenosis after cerebrovascular stent implantation. It has been reported (17) that STIM1 is a sensory receptor for calcium channel of calcium store controllability *in vivo*. The biological effects of cells are affected by controlling intracellular calcium concentration to regulate vasoconstriction. *In vitro* experiments have shown that CTRP9 can inhibit the proliferation of smooth muscle cells and angiogenesis and the formation of vascular new intima through Cyclic AMP (cAMP)-independent mechanism after injury of vascular (18). The increase of nitric oxide (NO) production promotes vasodilation and greatly improves endothelial cell function (19). These effects may be related to STIM1, CTRP9 and restenosis after cerebrovascular stenting. Therefore, this study investigated the effects of serum CTRP9 and STIM1 on restenosis after cerebrovascular stent implantation, and explored their relationship with vasoactive substances and inflammatory cytokines.

Based on the results of this study, serum CTRP9 level in group A was significantly lower than that in group B, and serum STIM1 level in group A was significantly higher than that in group B (all P<0.001), suggesting that serum CTRP9 low expression and STIM1 over-expression after cerebrovascular stent implantation may increase the risk of in-stent restenosis. When STIM1 expression is released, it inhibits the biological and homing functions of endothelial progenitor cells, directly damaging the repair of local vascular injury after stent implantation (20). According to a previous study (21), the increase of free fatty acids during tissue ischemia/reperfusion injury promotes the oxidative stress and increase of expression of CTRP9, and improves the metabolism function of the body to protect damaged myocardial cells, which is consistent with our results. The levels of serum NO, TNF-α and IL-6 in group A were significantly higher than those in group B (all P<0.001). Pearson results showed that serum CTRP9 level was positively correlated with NO and negatively correlated with TNF-α and IL-6. STIM1 was positively correlated with TNF-α and IL-6 and negatively correlated with NO (all P<0.001). The sustainable or controlled release of NO has diastolic effect on the endothelium and can repair and accelerate the vascular regeneration (22). TNF-α can regulate the expression of vasomotion substances and cause vasoconstriction after the decrease of the levels of vasorelaxation factors (23,24). It has been reported that IL-6 is involved in tissue fibrosis and induces the release of a large amount of inflammatory mediators under the effect of vascular endothelial tissue injury (25). In summary, serum TNF-α and IL-6 levels increase with vascular stenosis, while NO expression decreases. Combined with the results of CTRP9 and STIM1, the results of correlation between serum CTRP9, STIM1 levels and NO, TNF-α and IL-6 were inferred and confirmed, which further confirmed the predictive value of serum CTRP9 and STIM1 levels on restenosis after cerebrovascular stent implantation. The sensitivity of serum CTRP9 level in the diagnosis of restenosis after cerebrovascular stent implantation was 59.68%, and the specificity was 75.76%. The sensitivity of serum STIM1 level in diagnosis of restenosis after cerebrovascular stent implantation was 87.10% and the specificity was 46.97%. The sensitivity of serum CTRP9 and STIM1 levels in the combined diagnosis of restenosis after

cerebrovascular stent implantation was 90.32% and the specificity was 48.48%. It indicated that both CTRP9 and STIM1 may be involved in the disease process of pathophysiological mechanism of restenosis after cerebrovascular stent implantation. The regulation and protection of CTRP9 and STIM1 on cerebrovascular function result in abnormal changes of intravascular components after reversal. There is substantial heterogeneity in the influence of signaling pathways and action sites, and the emphasis indicates that metabolic regulation is also different. Synergistic combined detection may improve the diagnostic efficacy of cardiovascular and cerebrovascular diseases.

Based on previous studies and the results of this study, it can be learned that the decreased level of CTRP9 and increased level of STIM1 after cerebrovascular stent implantation are closely related to vascular formation, repair and re-endothelialization. However, there are some limitations in this study. The specific differences between the combined diagnosis of CTRP9 and STIM1 and the separate diagnosis are not discussed in detail. We did not rule out the interference of other factors on these indexes, and failed to use the two factors as early predictors of restenosis after cerebral vascular stenting. These are the research topics of the future study. However, the results of this study have preliminarily shown that CTRP9 and STIM1 may play a role in the early prevention of restenosis after cerebrovascular stent implantation, providing a new theoretical direction for the diagnosis and prognostic evaluation of restenosis after cerebrovascular stent implantation.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JP, XC and LZ conceived and designed the study. JP, GW, KX, JH and LZ were responsible for the acquisition, analysis and interpretation of the data. JP drafted the manuscript. XC and LZ revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Yantaishan Hospital (Yantai, China). Signed informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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