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Cluster of Differentiation 147 (CD147) serves as a promoter of atherosclerosis in patients with cerebral infarction

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Abstract. – OBJECTIVE: The aim of this study was to investigate the correlations of cluster of differentiation 147 (CD147) with plaque stability of carotid atherosclerosis (AS), degree of stenosis, inflammatory factors, matrix metalloproteinase-9 (MMP-9) expression and vascular endothelial function in patients with cerebral infarction.

PATIENTS AND METHODS: A total of 50 patients diagnosed with cerebral infarction (cerebral infarction group), 70 patients diagnosed with AS plaque (plaque group, with no infarction but plaques only) and 30 healthy people receiving physical examination (control group) in our hospital from March 2018 to July 2019 were collected. The levels of biochemical indexes, CD147, MMP-9, vascular endothelial function indexes [endothelin-1 (ET-1) and C-reactive protein (CRP)] and inflammatory factors [interleukin-10 (IL-10), IL-16 and tumor necrosis factor-alpha (TNF-α)] in the blood of each group of patients were detected *via* radioimmunoassay and enzyme-linked immunosorbent assay (ELISA). Moreover, ultrasonic examination and Gensini score system were applied to score the degree of carotid stenosis in cerebral infarction group. Finally, the differences in various parameters were compared among the three groups, and the correlations of CD147 with different indexes were evaluated using Spearman method.

RESULTS: Compared with those in control group, the levels of CD147, MMP-9, hemoglobin, platelets, total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), apolipoprotein A, apolipoprotein B, IL-10, IL-13 and TNF-α in the blood were remarkably elevated in cerebral infarction group and plaque group ($p<0.05$). Cerebral infarction group had notably higher levels of CD147, hemoglobin, triglyceride, apolipoprotein B, IL-10, IL-13 and TNF-α in the blood than plaque group ($p<0.05$). The plaque score was markedly higher in cerebral infarction group than that in plaque group [(3.27±2.86) points vs. (0.93±1.44) points] ($p<0.05$). In comparison with control group, plaque group and cerebral infarction group exhibited evidently raised levels of blood ET-1 and CRP ($p<0.05$). The serum CD147 level was significantly associated with MMP-9 ($p=0.003$, $r=0.616$), Gensini score ($p=0.006$, $r=0.656$), plaque score ($p=0.027$, $r=0.396$), IL-10 ($p=0.004$, $r=0.603$), TNF-α ($p=0.001$, $r=0.746$) and CRP ($p=0.037$, $r=0.450$) in cerebral infarction group.

CONCLUSIONS: CD147 level is prominently increased in carotid AS and closely related to inflammatory responses, and CD147 may become a new reference for the prediction and treatment of AS and cerebral infarction.

Key Words:
CD147, Cerebral infarction, Carotid atherosclerosis, Plaque, Inflammation, Blood vessels.

Introduction

Atherosclerosis (AS) is recognized as the most important pathological factor for stroke[1,2]. Several prospective studies[3,4] have revealed that carotid intima-media thickness (IMT) can independently predict future vascular events. Katsuumi et al[5] also demonstrated that AS plaques play a role in the risk of cerebrovascular accidents, and the treatment of carotid atherosclerotic stenosis can prevent the occurrence of cerebral infarction. Therefore, the severity of carotid stenosis induced by carotid AS plaques has been widely used as a radiographic index of stroke risk and a key index of AS treatment.

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Researching the key inflammatory mechanism of AS, a known type of inflammatory disease, is essential to design treatment strategies for cardiovascular diseases. Cluster of differentiation 147 (CD147), also named extracellular matrix metalloproteinase (MMPs) inducer or basigin, is not only a member of the immunoglobulin superfamily but also a well-known effective inducer of MMPs[6,7]. The expression level of CD147 differs in many cell types, including hematopoietic cells, epithelial cells, endothelial cells (ECs) and leukocytes[8]. CD147 was first discovered on the surface of solid tumor cells, and it has been found to interact with other isotypes of CD147 molecule, thus inducing the expression of various MMPs in adjacent fibroblasts[9]. CD147 is upregulated in inflammatory diseases. In fact, the overexpression of CD147 is observed in pulmonary inflammatory disease, rheumatoid arthritis, systemic lupus erythematosus and ischemic injury[10]. There is massive evidence that CD147 has potential functions in AS.

In the present study, the expression level of serum CD147 in 50 patients with cerebral infarction, 70 patients with AS plaque (merely plaque and no infarction) and 30 healthy physical examinees was detected, and its correlations with plaque stability, infarction area, inflammatory factors and vascular endothelial function were analyzed, so as to further understand the role of CD147 in AS and atherothrombosis and provide a new strategy for preventing and treating cardiovascular diseases.

Patients and Methods

Clinical Data

A total of 50 patients diagnosed with cerebral infarction (cerebral infarction group, with acute cerebral infarction and carotid plaques on the same side), 70 patients diagnosed with AS plaques (plaque group, with no infarction but carotid plaques only) and 30 healthy people receiving physical examination (control group, with no plaque) in our hospital from March 2018 to July 2019 were collected. The patients with cerebral infarction were examined by cranial CT or MRI and met the diagnostic criteria of cerebral infarction in Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2014. The exclusion criteria in each group were set as follows: 1) patients with acute coronary syndrome, heart failure or various severe congenital heart diseases, 2) those with autoimmune disease or other inflammatory diseases, 3) those with malignant tumor complicated with serious impairment of hepatic or renal function, 4) those with a past history of cerebrovascular disease within 6 months, 5) those complicated with intracerebral hemorrhage, cerebrovascular malformation, cerebral venous sinus thrombosis or other cerebral diseases, or 6) those with various acute/chronic infectious diseases. All enrolled patients and healthy physical examinees or their guardians signed the informed consent and provided blood samples, and the research processes conformed to the requirements of medical ethical and humanitarian requirements. This study was approved by the Ethics Committee of The Second Affiliated Hospital of Soochow University.

Measurement of Blood Indexes

Fasting venous blood (10 mL) was collected from the elbow of hospitalized patients on the next morning after admission, and from the healthy controls on the day of physical examination. Some of the venous blood samples obtained were used for blood routine test, biochemical marker test and routine coagulation test, while the other samples were put into coagulation-promoting tubes and fully mixed. Within 30 min after collection, the samples were centrifuged at 3,000 r/min and 2-8°C for 15 min, and the serum was aspirated and stored at -80°C for later use.

Horseradish peroxidase-labeled immune antibodies and sandwich Enzyme-Linked Immunosorbent (ELISA) were adopted to measure the levels of CD147, MMP-9, interleukin-10 (IL-10), IL-16 and tumor necrosis factor-alpha (TNF-α). The antibodies against CD147 (article number: DEMP00, R&D Systems, Minneapolis, MN, USA), MMP-9 (article number: DMP900, R&D Systems, Minneapolis, MN, USA), IL-10 (article number: DY417, R&D Systems, Minneapolis, MN, USA), IL-16 (article number: M1300CB, R&D Systems, Minneapolis, MN, USA) and TNF-α (article number: 210-TA, R&D Systems, Minneapolis, MN, USA) were coated in each well of a 96-well ELISA plate in strict accordance with the instructions.

Examination Methods

Philips HD11XE (L12-3 probe, probe frequency: 8-12 MHz) and GE LOGIQ7 color Doppler ultrasonic diagnostic apparatus (L10 probe, probe frequency: 8-10 MHz) were used for examination.

Interpretation of Ultrasonic Examination Results and Scoring of Carotid Plaques and Stenosis Degree

The diagnostic criteria of carotid plaques were as follows: the bilateral common carotid arteries and internal carotid arteries were detected, and

the IMT of the common carotid arteries was measured after the posterior wall of the part at 1 cm proximal to the carotid bifurcation was amplified. IMT>1.5 mm was defined as plaque formation.

Plaques were scored. The transverse and longitudinal sections were judged comprehensively, the number, length and thickness of the plaques were observed and recorded, and the texture and shape of the plaques were observed from multiple angles. The plaques were scored from the following aspects: 1) homogeneity of plaques (consistency of echo): 0 points (homogeneous plaques) and 1 point (inhomogeneous plaques); 2) plaque thickness: 0 points (<2 mm), 1 point (2-3 mm) and 2 points (>3 mm); 3) plaque length: 0 points (<15 mm) and 1 point (≥15 mm). 4) If the plaques caused vascular stenosis, the stenosis would be evaluated as 3 points (50-69% of stenosis) or 4 points (70-99% of stenosis), and the score was not recorded together with that of plaque thickness. 5) As for the morphology of plaques, the interruption of fibrous caps, visible thrombosis and large depression on the surface of plaques were marked 3 points, while the regular morphology was scored 0 points. Finally, the sum of the scores of all measurable plaques in ipsilateral common carotid artery and internal carotid artery was taken as the score of unilateral carotid plaques. The score of carotid plaques on the contralateral side of acute infarction focus was recorded in cerebral infarction group, and that of bilateral carotid plaques was recorded in plaque group.

In terms of the scoring of stenosis degree, the Gensini score system[11] was applied to assess the degree of carotid lesions, including 1 point (<25% stenosis), 2 points (25-49% stenosis), 4 points (50-74% stenosis), 8 points (75-89% stenosis), 16 points (90-99% stenosis) and 32 points (100% stenosis/complete occlusion).

Statistical Analysis

The experimental results were analyzed using GraphPad Prism software (Version 5.01, GraphPad Company, Santiago de Chile, La Jolla, CA, USA). The measurement data were expressed as ($\bar{\chi}$±s). As for the comparison of the measurement data between two groups, *t*-test was performed for normally distributed data, while nonparametric Mann-Whitney U test was used for the data not in line with normal distribution. The linear relationship between variables was examined by Spearman correlation analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of CD147, MMP-9 and Relevant Biochemical Indexes in the Blood Among the Three Groups

Compared with those in control group, the levels of CD147, MMP-9, hemoglobin, platelets, total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), apolipoprotein A and apolipoprotein B in the blood were remarkably elevated in plaque group and cerebral infarction group ($p<0.05$) (Table I). Moreover, cerebral infarction group had notably higher levels of CD147, hemoglobin, triglyceride and apolipoprotein B in the blood than plaque group, and the differences were statistically significant ($p<0.05$).

Table I. Comparisons of CD147 and relevant biochemical indexes in the blood among the three groups.

Index	Control group (n=30)	Plaque group (n=70)	Cerebral infarction group (n=50)
CD147 (ng/mL)	4.23±2.36	9.12±6.21*	15.88±12.06*#
MMP-9 (ng/mL)	3.83±1.28	12.43±6.43*	14.32±8.33*
Hemoglobin (g/L)	86.76±31.27	143.26±33.43*	161.32±46.12*
Platelets (10^9/L)	224.38±62.91	315.76±56.29*	338.40±52.38*
Leukocyte (10^9/L)	4.83±2.38	6.27±2.66	6.75±4.62
Total cholesterol (mmol/L)	4.77±1.83	7.62±1.70*	8.38±1.28*
Triglyceride (mmol/L)	1.52±1.25	5.68±1.24*	13.92±1.03*#
LDL (mmol/L)	2.45±0.74	4.49±1.71*	5.52±1.38*
HDL (mmol/L)	1.16±0.37	3.27±1.28*	4.34±2.36*
Apolipoprotein A (g/L)	1.66±0.67	3.76±0.87*	4.47±0.94*
Apolipoprotein B (g/L)	1.47±0.56	3.92±2.84*	7.76±6.42*#

Note: *$p<0.05$: a statistically significant difference vs. control group, and #$p<0.05$: a statistically significant difference *vs.* plaque group.

Table II. Expressions of vascular endothelial function indexes in the plasma of three groups of patients.

Group	Control group (n=30)	Plaque group (n=70)	Cerebral infarction group (n=50)
ET-1 (ng/L)	45.85±15.08	81.34±21.65*#	120.14±31.52*#
CRP (mg/L)	3.44±0.87	24.19±16.56*	56.83±2.24*#

Note: *p<0.05: a statistically significant difference *vs.* control group, and #p<0.05: a statistically significant difference *vs.* plaque group.

Changes in Vascular Endothelial Function Indexes Endothelin-1 (ET-1) and C-reactive Protein (CRP) Levels in the Three Groups

In comparison with control group, plaque group and cerebral infarction group exhibited evidently raised levels of blood ET-1 and CRP (p<0.05), and they were higher in cerebral infarction group than those in plaque group (p<0.05) (Table II).

Comparisons of Serum Inflammatory Factors IL-10, IL-16 and TNF-α Among the Three Groups

As shown in Figure 1, the levels of serum IL-10, IL-13 and TNF-α rose distinctly in plaque group and cerebral infarction group compared with those in control group (p<0.05). Moreover, cerebral infarction group displayed prominently higher levels of serum IL-10, IL-13 and TNF-α than plaque group (p<0.05).

Comparison of Plaque Score Between Plaque Group and Cerebral Infarction Group

The score of plaques in internal carotid arteries and common carotid arteries on corresponding sides of foci was compared between plaque group and cerebral infarction group. The mean plaque score was increased markedly in cerebral infarction group in contrast with that in plaque group [(3.27±2.86) points *vs.* (0.93±1.44) points] (p<0.05), suggesting that the instability of carotid plaques is closely correlated with the occurrence of cerebral infarction (Figure 2).

Analysis Results of Correlations of CD147 Expression With Plaque Score, Inflammatory Factors, MMP-9 Content and Related Vascular Endothelial Function Indexes in Cerebral Infarction Group

The expression of serum CD147, plaque score, inflammatory factors, MMP-9 content and related vascular endothelial function indexes in cerebral infarction group were subjected to statistical analysis. The CD147 expression was significantly associated with MMP-9 (p=0.003, r=0.616), Gensini score (p=0.006, r=0.656), plaque score (p=0.396, r=0.523), IL-10 (p=0.004, r=0.603), TNF-α (p=0.001, r=0.746) and CRP (p=0.037, r=0.450) in cerebral infarction group (Table III and Figure 3).

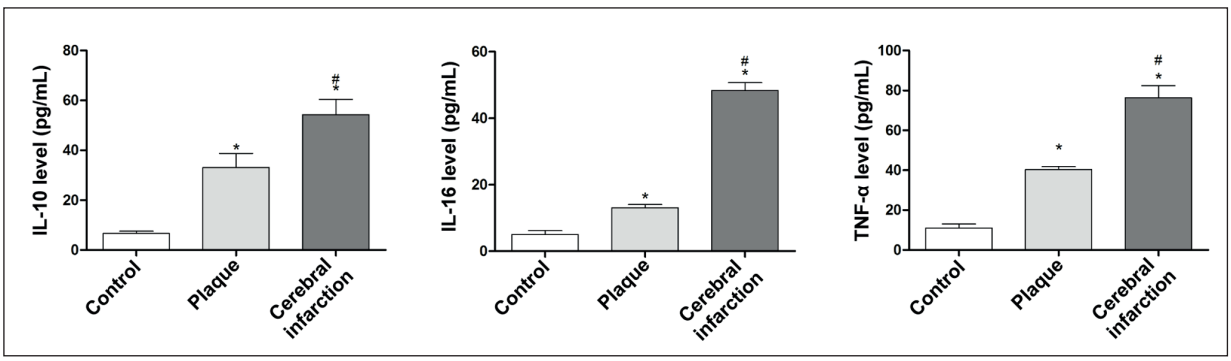

Figure 1. Comparisons of inflammatory factors IL-10, IL-16 and TNF-α in the serum among the three groups. Note: *p<0.05: a statistically significant difference *vs.* control group, and #p<0.05: a statistically significant difference *vs.* plaque group. The levels of serum IL-10, IL-13 and TNF-α were remarkably higher in plaque group and cerebral infarction group than those in control group (p<0.05).

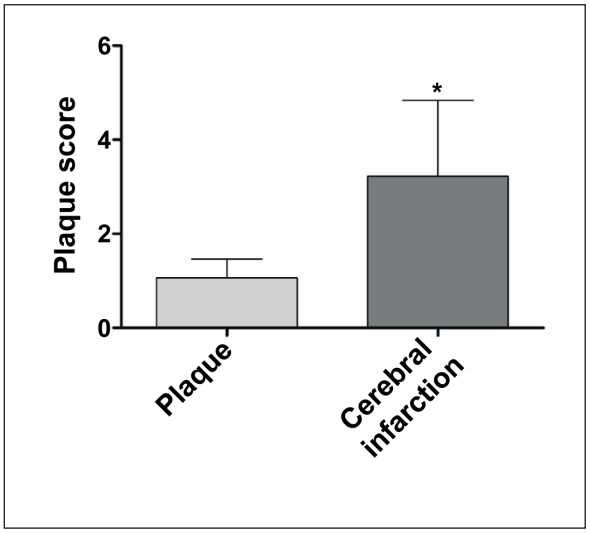

Figure 2. Comparison of plaque score between plaque group and cerebral infarction group. Note: *p<0.05: a statistically significant difference vs. plaque group. The plaque score was markedly higher in cerebral infarction group than that in plaque group (p<0.05).

Discussion

In the past, AS was regarded as the consequence of passive lipid accumulation on vessel walls. However, it is generally believed that AS is a chronic inflammation in the vascular endothelium under the action of multiple inflammatory factors at present, and it results from the complex interactions among diverse oxidative stress factors, such as hypertension, hyperglycemia and hyperlipidemia. After the onset of cerebral infarction, a severe outcome of AS, the infiltration of various inflammatory cells (neutrophils, macrophages, lymphocytes, etc.) and the secretion of inflammatory cytokines (e.g., ILs, CRP, TNF-α and MMPs) induce inflammatory cascades, thus aggravating brain tissue necrosis in the ischemic area[12]. Both thrombus and inflammatory pathways are crucial players in the development of arterial diseases. As a member of the immunoglobulin superfamily, CD147 is expressed in multiple cell types, including hematopoietic cells, ECs, leukocytes, keratinocytes and platelets. Recent evidence has indicated that CD147 has important effects on thrombosis, inflammation and cancer progression.

Increased CD147 expression is detected by Ni et al[13] in human AS plaques, mainly in regions rich in macrophages, SMCs and MMP-9-positive cells. Heinzmann et al[14] reported that CD147 and its receptor CyPA are co-expressed in the EC layer facing the lumen and macrophage-enriched regions. Clinical data[15] have demonstrated that the level of CD147 is elevated in the platelets, monocytes and granulosa cells of patients with coronary artery disease. All these findings suggest that CD147 may significantly contribute to the pathological processes of AS and atherothrombosis. Hence, this investigation aims to explore the relations of CD147 with the formation and stability of carotid plaques. People with and without cerebral infarction were researched separately because the local inflammatory responses triggered by cerebral infarction itself will affect the content of CD147. In this paper, the association between CD147 and plaque formation was revealed through the comparisons between non-plaque group (with no plaques and infarction) and plaque group (with no infarction but merely plaques). The results manifested that there were significant differences in the CD147 level among control group, plaque group and cerebral infarction group, implying that CD147 has a correlation with plaque formation. In addition, such a correlation was showed by the associations of CD147 with the score and area of infarction.

Table III. Analysis of correlations of CD147 expression with plaque score, inflammatory factors, MMP-9 content and related vascular endothelial function indexes in cerebral infarction group.

Item	Mean value in cerebral infarction group	Correlation coefficient (r)	p
MMP-9 (ng/L)	14.32±8.33	0.616	0.003
Gensini score	7.35±3.23	0.656	0.006
Plaque score	3.27±2.86	0.396	0.027
IL-10 (pg/mL)	41.48±15.21	0.603	0.004
IL-16 (pg/mL)	46.63±12.63	0.125	0.173
TNF-α (pg/mL)	64.41±18.05	0.746	0.001
ET-1 (ng/L)	120.14±31.52	0.147	0.462
CRP (mg/L)	56.83±12.24	0.450	0.037

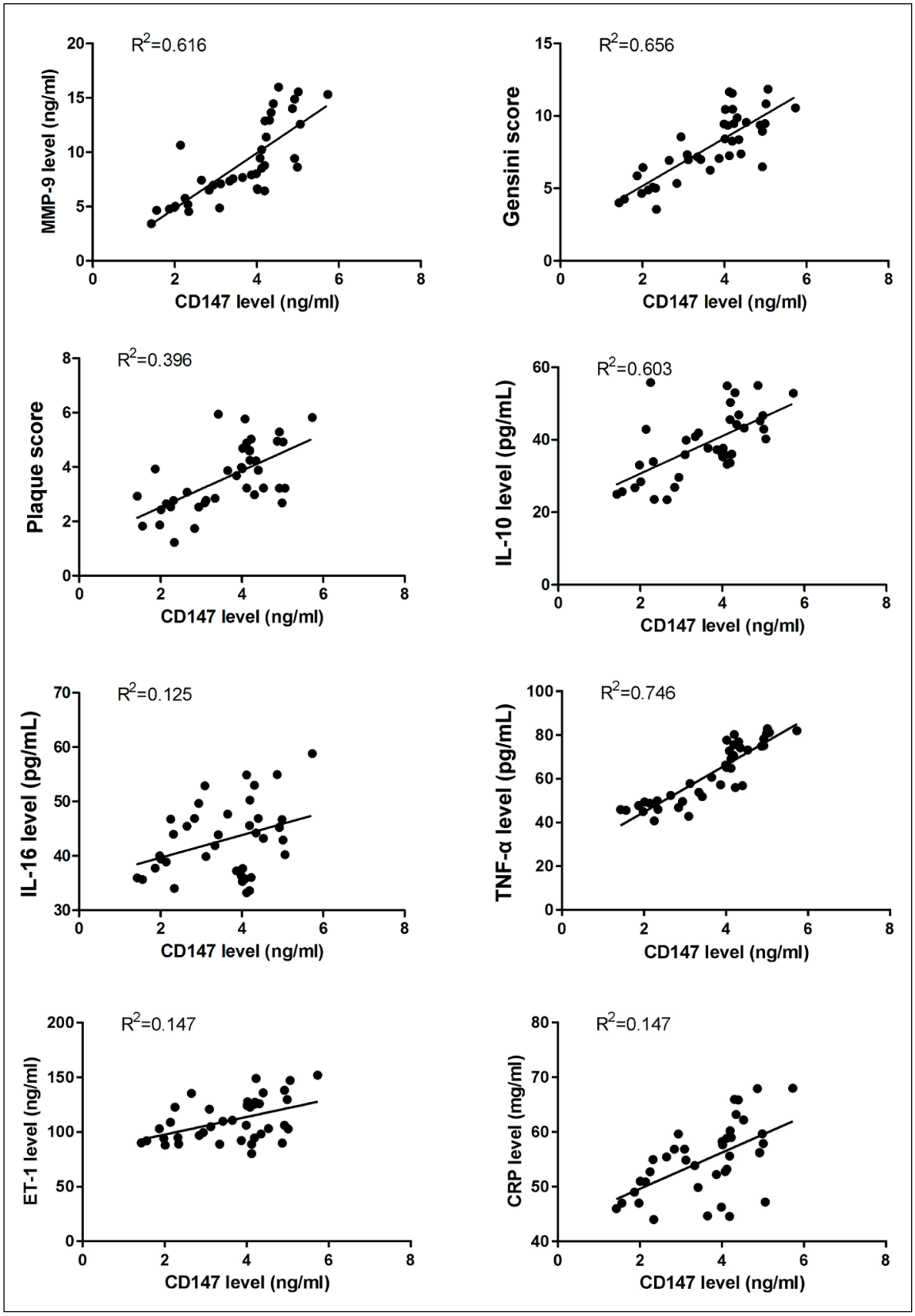

Figure 3. Analysis of correlations of CD147 expression with plaque score, inflammatory factors, MMP-9 content and related vascular endothelial function indexes in cerebral infarction group.

Platelet activation is involved in the pathogenesis of AS and thrombosis. It was found in this study that the level of platelets was increased markedly in plaque group and cerebral infarction group. Zong et al[16] revealed that CD147 is located in the open canalicular system of alpha granules and platelets, which is upregulated by various platelet stimuli (thrombin, ADP and collagen), and then, transferred onto the exterior surface of cells. Based on *in vitro* data, diversified factors and products, such as LDL, CRP, advanced glycation end products and high glucose level, can stimulate the expression of CD147 in inflammatory cells, ultimately promoting AS[17]. Anti-atherosclerotic drugs, such as fluvastatin are capable of inhibiting the CD147 expression in macrophages[18]. Moreover, the CD147 expression in platelets is able to facilitate the nuclear factor-kappa B (NF-κB)-dependent inflammatory processes in monocytes. Wang et al[19] have indicated that the incubation of platelets with monocytes can induce the expressions of NF-κB-dependent inflammatory cytokines (e.g., IL-6 and TNF-α) and MMP-9 in monocytes by means of CD147, which can be decreased by pretreatment with CD147 si-RNA or blocking antibody. Consistently, it was discovered in the present study that cerebral infarction group had notably higher levels of serum IL-10, IL-13 and TNF-α than plaque group and control group, and the correlation analysis also manifested that the CD147 content was intimately related to the levels of inflammatory factors IL-10 (p=0.004, r=0.603), TNF-α (p=0.001, r=0.746) and CRP (p=0.037, r=0.450). More importantly, it has been revealed that CD147 is able to interact with a variety of proteins, including cyclophilin, and exerts crucial effects in platelet activation and recruitment[20].

Conclusions

Altogether these data indicate that CD147 level is prominently increased in carotid AS and closely related to inflammatory responses. Our findings could provide for the first time a potential strategy for preventing and treating cardiovascular diseases. However, the dynamic changes in relevant indexes in patients after admission to hospital were not fully presented due to a single time node in this study. Therefore, clinical studies with a larger sample size will be conducted to further determine the changes of CD147 in AS in the future.

Conflict of Interests

The authors declared no conflict of interest.

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