Research Article

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Serum tumor marker carbohydrate antigen 125 levels and carotid atherosclerosis in patients with coronary artery disease

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Abstract: Objective: We assessed the correlation between serum carbohydrate antigen 125 (CA125) and carotid intima-media thickness (cIMT) in patients with coronary artery disease (CAD). Methods: We collected 518 CAD patients from the cardiovascular disease center in our hospital, and all cIMT values were measured in patients with CAD. Results: The serum CA125 concentrations were found to be increased in CAD patients with early carotid atherosclerosis compared with patients without early carotid atherosclerosis (20.1±7.7 vs. 17.7±6.4 U/mL, p<0.001). The cIMT values were increased in patients with higher serum CA125 levels than those with lower serum CA125 concentrations (1.16±0.32 vs. 0.98±0.29 mm, p<0.001). There was a positive correlation between serum CA125 and cIMT in CAD patients (r=0.262, p<0.001). Moreover, the serum CA125 concentrations also were positively correlated with cIMT in subjects with early carotid atherosclerosis and without early carotid atherosclerosis (r=0.255, p<0.001; r=0.189, p=0.002). We found that serum CA125 concentrations were independently correlated with cIMT (beta = 0.293, p<0.001) in multiple linear regression analysis. Conclusions: We found that serum CA125 concentrations were positively correlated with cIMT in CAD patients, serum CA125 might be a potential biochemical marker for the estimation of atherosclerosis in patients with CAD.

Keywords: Serum carbohydrate antigen 125; Carotid intima-media thickness; Coronary artery disease

1 Materials and methods

We collected 518 CAD patients from the cardiovascular disease center in the First Affiliated Hospital, Xinjiang
Medical University. The diagnosis of CAD was determined by coronary angiography in all patients. Patients with following conditions were excluded: liver dysfunction, chronic obstructive pulmonary disease, aortic dissection, immune diseases, acute and chronic infections, malignant tumor and psychosis. All the subjects completed the clinical examinations, including anthropometric assessments, carotid ultrasonography examinations and laboratory tests. The study was approved by the ethics committee of the First Affiliated Hospital, Xinjiang Medical University.

We collected information about physical examinations such as age, gender, body mass index (BMI) and drug use histories. Fast plasma glucose (FPG), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) levels were tested by using automatic biochemistry analyzer. High-sensitivity C-reactive protein (hs-CRP) concentrations were tested by automatic immune analyzer. In addition, serum CA125 levels were measured with chemiluminescent analyzer. The cIMT values were obtained from ultrasonic examination results.

2 Statistics analysis

The data analyses were performed by using 19.0 SPSS software (SPSS Inc., Chicago, IL, USA). Continuous variables and categorial variables were presented as mean±standard deviation and proportions, repectively. Differences between two groups were analyzed by using the Student’s t test, U test and Chi-square test. The correlation between CA125 and cIMT in patients CAD was analyzed by Pearson or Spearman method. Multivariate linear regression was used to further evaluate this link between CA125 and cIMT. P values of less than 0.05 were accepted as significant.

3 Results

3.1 The clinical characteristics in all patients with CAD

The study population consisted of 518 patients with CAD. The mean cIMT values were 1.1±0.31 mm. Further, when the concentrations of serum CA125 were divided by the median, the cIMT values were increased in patients with higher serum CA125 levels than those with lower serum CA125 concentrations (1.16±0.32 vs. 0.98±0.29 mm, p<0.001).

3.2 The serum CA125 concentrations divided by the threshold of cIMT values

We decided to divide all patients with CAD into two groups: subjects with early carotid atherosclerosis (cIMT > 1.0 mm) and without early carotid atherosclerosis (cIMT ≤ 1.0 mm). The serum CA125 concentrations were found to be increased in CAD patients with early carotid atherosclerosis compared with patients without early carotid atherosclerosis (20.1±7.72 vs. 17.7±6.41 U/mL, p<0.001). There were statistical differences for age, body mass index, diabetes mellitus, anti-platelet agent use and high-sensitivity C-reactive protein, as shown in Table 1.

3.3 The correlation analysis between serum CA125 and laboratory indexes

The correlation analysis showed that serum CA125 concentrations were positively correlated with BMI, LDL-C, Cr and hs-CRP in patients with CAD (r=0.113, p=0.010; r=0.095, p=0.031; r=0.098, p=0.026; r=0.124, p=0.005) (Table 2). There was a positive correlation between serum CA125 and cIMT in CAD patients (r=0.262, p<0.001) (Figure 1). Moreover, we assessed the correlations between serum CA125 and cIMT in subjects with early carotid atherosclerosis and without early carotid atherosclerosis, the serum CA125 concentrations also were positively correlated with cIMT in the two groups (r=0.255, p<0.001; r=0.189, p=0.002).

3.4 Multiple linear regression analysis between serum CA125 and cIMT in all patients

In the multiple linear regression analysis, adjustment for sex, age, BMI, blood glucose, LDL-C, HDL-C, TC, TG, hs-CRP, ALT, AST, diabetes mellitus, hypertension and medications uses, we found that serum CA125 concentrations were independently correlated with cIMT (beta = 0.293, p<0.001) in multiple linear regression analysis (Table 3). The correlation between serum CA125 and cIMT in all patients with CAD reappeared when cIMT variable was included in dependent variable in the multiple linear regression analysis (beta=0.258, p<0.001) (Table 4).
4 Discussion

The cIMT measurements have been recommended as a screening method for high-risk populations with cardiovascular events such as older adults, type 2 diabetes mellitus and systemic lupus erythematosus [19-21]. There was evidence that cIMT is an independent predictor of stroke in persons without a history of cardiovascular disease [22]. In addition, serum CA125 has been associated with the diagnosis and prognosis of tumor diseases such as ovarian cancer [1], variant prostate carcinoma [3], non-Hodgkin's lymphoma [23]. Interestingly, our study

| Table 1: Clinical and laboratory parameters in with and without early carotid atherosclerosis |
|---------------------------------------------------------------|
|                                      | >1.0 N=262 | ≤1.0 N=256 | p-values |
| Gender (M)                                  | 222(84.7%) | 203(79.3%) | 0.107 |
| Age(yr)                                    | 55.8±13.07 | 48.5±8.96  | <0.001 |
| Body mass index (kg/m2)                    | 23.9±3.01  | 23.1±2.80  | 0.009 |
| Diabetes mellitus                          | 102(38.9%) | 75(29.3%)  | 0.021 |
| Hypertension                                | 116(44.3%) | 103(40.2%) | 0.352 |
| Calcium channel blockers                    | 27(10.3%)  | 16(6.2%)   | 0.094 |
| Anti-platelet agent use                     | 259(98.9%) | 239(93.4%) | 0.001 |
| Nitrates                                   | 156(59.5%) | 164(64.1%) | 0.290 |
| B-blockers                                  | 213(81.3%) | 195(76.2%) | 0.154 |
| ACEI/ARB                                    | 223(85.1%) | 225(87.9%) | 0.355 |
| Alanine transaminase (U/L)                  | 17.4±7.81  | 16.6±7.32  | 0.256 |
| Aspartate transaminase (U/L)                | 18.0±4.55  | 17.9±4.83  | 0.772 |
| Low density lipoprotein cholesterol (mmol/L) | 2.5±0.87  | 2.5±0.84  | 0.471 |
| High density lipoprotein cholesterol (mmol/L) | 1.2±0.32  | 1.2±0.34  | 0.796 |
| Total cholesterol (mmol/L)                  | 4.1±1.12   | 4.0±1.01   | 0.318 |
| Triglycerides (mmol/L)                      | 1.0±0.33   | 1.0±0.37   | 0.348 |
| Blood glucose (mmol/L)                      | 5.6±2.06   | 5.4±1.88   | 0.244 |
| High sensitivity C-reactive protein (mg/L)  | 1.8±1.74   | 1.5±1.49   | 0.025 |
| Creatinine (umol/L)                         | 64.6±17.22 | 65.0±17.20 | 0.803 |
| Serum carbohydrate antigen 125 (U/mL)       | 20.1±7.72  | 17.7±6.41  | <0.001 |

| Table 2: The correlation between serum CA125 and laboratory parameters in all patients |
|---------------------------------------------------------------|
| Items                                    | r      | p-values |
|---------------------------------------------------------------|
| Body mass index                           | 0.113  | 0.010    |
| High sensitivity C-reactive protein        | 0.124  | 0.005    |
| Low-density lipoprotein cholesterol        | 0.095  | 0.031    |
| Creatinine                                | 0.098  | 0.026    |
| Carotid intima-media thickness            | 0.262  | <0.001   |

Figure 1: Serum CA125 concentrations and cIMT in the patients with CAD
first found that the increased serum CA125 concentrations were positively correlated with cIMT in the study population, and serum CA125 may be a well marker for subclinical atherosclerosis in patients with CAD. However the mechanism for the correlation between serum CA-125 concentrations and cIMT still remains unclear. Inflammation may contribute to explain this relationship. It is known that the atherosclerosis is considered to be the accumulation of lipoproteins and the stimulation of inflammation in the arterial wall, and low-density lipoprotein molecules are the main inducement for the pathological processes [24]. Indeed, the inflammation plays a key role in the regulation of the atherosclerotic development. Some studies have shown that some inflammatory cytokines were related with carotid atherosclerosis [25]. The production of CRP has been found to promote the formation of atherosclerosis directly [26]. Recent studies have found that serum CA125 concentrations were related to inflammatory cytokines in patients with heart failure and atrial fibrillation, such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), and increased CA125 levels might be the activation of inflammatory cytokines in the early stages of atherosclerosis [9, 27-28]. Therefore, the inflammatory conditions may increase serum CA125 concentrations in patients with CAD, and links the relationship between serum CA125 and cIMT in study subjects.

The screening and detection of subclinical atherosclerosis is a primary prevention, which can reduce the occurrence of cardiovascular events. Compared with carotid ultrasound, serum CA125 is an objective and convenient biochemical parameter, which is rarely affected by subjective factors. In our study, we found correlation between serum CA125 and cIMT in patients with CAD. Therefore, we believe that serum CA125 may provide useful information for the assessment of atherosclerosis in patients with CAD.

We noted several limitations in this study. First, a longitudinal study is needed to assess the relationship between serum CA125 and cIMT in patients with CAD. Second, our study did not assess the link of serum CA125 and clinical outcomes in patients with CAD. Finally, the present study did not provide the evidence between serum CA125 and anti-inflammatory treatments in patients with CAD. In conclusion, we found that serum CA125 concentrations were positively correlated with cIMT in CAD patients, and serum CA-125 may be a potential biochemical marker for the atherosclerosis in patients with CAD.

**Interest declarations:** The authors have no financial conflicts of interes.
References

[1] van der Burg ME, Lammes FB, Verweij J. Cance CA 125 in ovarian cancer. Neth J Med. 1992 Feb; 40(1-2):36-51
[2] Moss EL, Hollingworth J, Reynolds TM. The role of CA 125 in clinical practice. J Clin Pathol. 2005 Mar; 58(3):308-312
[3] Erdile LF, Smith D, Berd D. Whole cell ELISA for detection of tumor antigen expression in tumor samples. J Immunol Methods. 2001 Dec 1;258(1-2):47-53
[4] Zacharos ID, Efstadthiou SP, Petreli E, Georgiou G, Tsiooulos DI, Mastorantonakis SE, Christakopoulou I, Roussou PP. The prognostic significance of CA 125 in patients with non-Hodgkin’s lymphoma. Eur J Haematol. 2002 Oct;69(4):221-226
[5] Camera A, Villa MR, Rocca S, De Novellis T, Costantini S, Pezzullo L, Lucania A, Mariano A, Macchia V, Rotoli B. Increased CA 125 serum levels in patients with advanced acute leukemia with serosal involvement. Cancer. 2000 Jan 1;88(1):75-78
[6] Peng T, Guo L, Xia Q, Yang X. Clinical significance of serum CA125 in nephrotic syndrome. Clin Lab. 2012;58(1-2):113-115
[7] Qureshi MO, Dar FS, Khokhar N. Cancer Antigen-125 as a marker of ascites in patients with liver cirrhosis. J Coll Physicians Surg Pak. 2014 Apr;24(4):232-235. doi: 04.2014/JCPSP.232235
[8] Candocia SA, Locker GY. Elevated serum CA 125 secondary to tuberculous peritonitis. Cancer. 1993 Sep 15;72(6):2016-2018
[9] Turgut O, Tandogan I, Yilmaz MB, Gul I, Zorlu A. CA125 in heart failure: implications for immune-inflammatory activity. J Coll Physicians Surg Pak. 2011 Jan 7; 146(1):99-100. doi: 10.1016/j.ijcard.2010.05.077
[10] Falcão F, de Oliveira FRA, da Silva MCFC, Sobral Filho DC. Carbohydrate antigen 125: a promising tool for risk stratification in heart diseases. Biomark Med. 2018 Apr;12(4):367-381
[11] Jong X, Yunke Z, Guoping L, Zhenyue C. Clinical and prognostic value of elevated CA125 levels in patients with coronary heart disease. Herz. 2015 Jun;40(4):690-694
[12] Ikonomidou I, Makavos G, Lekakis J. Arterial stiffness and coronary artery disease. Curr Opin Cardiol. 2015 Jul;30(4):422-31. doi: 10.1097/HCO.0000000000000179
[13] Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011; 123:e18-e209
[14] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation 2007; 115: 459-467
[15] Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation. 1997; 96: 1432-1437
[16] O’Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999; 340: 14-22
[17] Eversen K, Sarvari SI, Ranning OM, Edvardsen T, Russell D. Carotid artery intima-media thickness is closely related to impaired left ventricular function in patients with coronary artery disease: a single-centre, blinded, non-randomized study. Cardiovasc Ultrasound. 2014 Sep 29;12:39
[18] Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incidence of stroke is related to carotid IMT even in the absence of plaque. Atherosclerosis, 2005; 179: 325-331
[19] Pickhart M, Celermaier DS, Zureik M, Helmer C, Jouven X, Ritchie K, Tzouri C, Ducimetière P, Empana JP. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. The Three-City Study. Atherosclerosis. 2011 Dec;219(2):917-24. doi: 10.1016/j.atherosclerosis.2011.09.024
[20] Yeboah J, Erbel R, Delaney JC, Nance R, Guo M, Bertoni AG, Budoff M, Moebus S, Jöckel KH, Burke GL, Wong ND, Lehmann N, Herrington DM, Mühlenkamp S, Greenlan P. Development of a new diabetes risk prediction tool for incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study. Atherosclerosis. 2014 Oct;236(2):411-7. doi: 10.1016/j.atherosclerosis.2014.07.035
[21] Scalzi LV1, Bhatt S, Gilkeson RC, Shaffer ML. The relationship between race, cigarette smoking and carotid intimal medial thickness in systemic lupus erythematosus. Lupus. 2009 Dec;18(14):1289-97. doi: 10.1177/0961203309345781
[22] Chien KL, Su TC, Jeng JS, Hsu HC, Chang WT, Chen MF, Lee YT, Hu FB. Carotid artery intima-media thickness, carotid plaque and coronary heart disease and stroke in Chinese. PloS One. 2008;3(10):e3435. doi: 10.1371/journal.pone.0003435
[23] Zacharos ID, Efstadthiou SP, Petreli E, Georgiou G, Tsiooulos DI, Mastorantonakis SE, Christakopoulou I, Roussou PP. The prognostic significance of CA125 in patients with non-Hodgkin’s lymphoma. Eur J Haematol. 2002 Oct;69(4):221-226
[24] Steinberg D. The LDL modification hypothesis of atherosclerosis: an update. J Lipid Res. 2009 Apr;50 Suppl:S376-81. doi: 10.1194/jlr.R800087-JLR200
[25] Kosaka T, Kobuko Y, Ono T, Sekine S, Kida M, Kikui M, Yamamoto M, Watanabe M, Amano A, Maeda Y, Miyamoto Y. Salivary inflammatory cytokines may be novel markers of carotid atherosclerosis in a Japanese general population: the Suita study. Atherosclerosis. 2014 Nov;237(1):123-128
[26] Bian F, Yang X, Zhou F, et al. C-reactive protein promotes atherosclerosis by increasing LDL transcytosis across endothelial cells. Br J Pharmacol. 2014 May;171(10):2671-2684
[27] Huang F, Chen J, Liu Y, Zhang K, Wang J, Huang H. New mechanism of elevated CA125 in heart failure: the mechanical stress and inflammatory stimuli initiate CA125 synthesis. Med Hypotheses. 2012 Sep;79(3):381-383
[28] Hamdy NM. Relationship between pro-anti-inflammatory cytokines, T-cell activation and CA 125 in obese patients with heart failure. Med Sci Monit. 2011 Feb 25;17(3):CR174-179