MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 2873-2877
DOI: 10.12659/MSM.907418

Received: 2017.10.05
Accepted: 2017.11.07
Published: 2018.05.07

Relationship Between Carbohydrate Antigen 125 and Coronary Artery Calcification in Patients without Known Coronary Artery Disease

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Statistical Analysis C
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Source of support: Departmental sources

Background: This study was designed to investigate the association between serum carbohydrate antigen 125 (CA125) and coronary artery calcification (CAC) score in patients without known coronary artery disease.

Material/Methods: The study groups included 348 consecutive subjects with chest pain but without known coronary artery disease, and who underwent an estimation of CAC score in our hospital.

Results: The clinical and laboratory characteristics of all subjects are presented according to serum CA125 concentrations tertiles. The CAC score was found to be increased in the tertiles (31.6 ±82.10, 73.3±125.6, 122.9±135.9 U/mL, p<0.001). Serum CA125 concentrations are increased in calcium-positive patients compared with calcium-negative ones (9.3±4.79 *vs.* 11.2±7.36, p=0.003). A positive correlation between serum CA125 and CAC score was observed (r=0.319, p<0.001) in all participants. Similarly, the serum concentrations of CA125 were found to be positively correlated with CAC score in both women and men (r=0.328, p<0.001; r=0.265, p=0.001, respectively). Multiple linear regression analysis results indicated that serum CA125 concentrations are independently related to CAC score in the study population (beta=0.173, p=0.001), and age, sex, diabetes mellitus, and high-sensitivity C-reactive protein (hs-CRP) were also associated with CAC score in multiple linear regression analysis.

Conclusions: Serum CA125 concentrations are correlated with CAC score in the population without known coronary artery disease, and serum CA125 may be considered as a marker to estimate CAC in the study population.

MeSH Keywords: Angioplasty, Balloon, Coronary • CA-19-9 Antigen • Internal Mammary-Coronary Artery Anastomosis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/907418

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Background

Coronary artery calcification (CAC) is a part of the atherosclerotic processes and a traditional risk factor of cardiovascular disease in diverse subsets of the population [1]. CAC score has been reported to be linked with coronary artery disease and cardiovascular events [2]. A significant association of the presence of CAC with atherosclerosis burden has been demonstrated by Sangiorgi [3]. Recent studies have demonstrated that CAC is associated with increased morbidity and mortality in patients with chronic obstructive pulmonary disease [4], and is related with mortality in dialysis patients [5]. CAC examined by computerized tomography is a crucial marker of atherosclerotic presence, and is associated with coronary plaque burden [6,7]. Thus, an early estimation of CAC will assist in predicting increased mortality and morbidity in this patient population.

Carbohydrate antigen 125 (CA125) is regarded as a valuable marker for detecting ovarian cancer and predicting patient prognosis [5]. In addition to routine use in clinical ovarian tumors, it has recently been suggested that serum CA125 concentrations are associated with liver cirrhosis, deep endometriosis, and preeclampsia [8–10]. A positive correlation between serum CA125 concentrations and C-reactive protein (CRP) also was found in patients with preeclampsia [11]. On the other hand, increased CA125 concentrations have been reported in patients with heart failure [12]. Higher CA-125 concentrations have been found to be linked with new-onset atrial fibrillation in healthy postmenopausal females [13]. The serum levels of CA-125 can be used to predict the appearance of atrial fibrillation in heart failure patients [14]. Inflammation may be an important factor explaining the associations of serum CA125 with these diseases. Systemic inflammation contributes to the appearance of CAC, and promotes the development of CAC, even in the general population [15], and there are no data to estimate the relationship between serum CA125 and CAC in any population. Therefore, the present study was designed to investigate the association between serum CA125 and CAC scores in patients without known coronary artery disease.

Material and Methods

The study groups included 348 consecutive subjects with chest pain but without known coronary artery disease, and who underwent an estimation of CAC score in our hospital between January 2017 and September 2017. Exclusion criteria were: heart failure, coronary artery disease (including stenocardia and myocardial infarction), atrial fibrillation, cardiomyopathies, renal and liver dysfunction, hemolytic disorders, thyroid disease, acute and chronic inflammatory diseases, neoplastic diseases, immune diseases, current or former smoking, and pregnant woman. Patients who underwent any stress test or coronary angiography before CAC assessment were excluded. The study was approved by the Beijing Aerospace General Hospital Institutional Review Board, and informed consent was obtained from all participants.

Clinical and laboratory data

Fasting blood samples were obtained within 2 h. The laboratory parameters were tested in a single laboratory, including fasting blood glucose (FBG), total protein (TP), alanine transaminase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-sensitivity C-reactive protein (hs-CRP), creatinine (Cr), urea nitrogen (UN), and CA125. Clinical information was obtained from medical records, including sex, age, body mass index (BMI), and other data. All computerized tomography scans were performed on a 128-slice scanner for generating CAC scores.

Statistical analysis

All statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as percentages or means ± standard deviation, as appropriate. The one-way ANOVA test and chi-square test were used to compare the differences between the 3 groups. The correlations of CA125 with clinical, laboratory, and CAC score were assessed by Pearson or Spearman analysis. Multiple linear regression analysis was used to assess the independent variables affecting the relationship between serum CA125 concentrations and CAC score in the study population. Two-tailed $P<0.05$ was considered as indicating statistically significant differences.

Results

The clinical and laboratory characteristics of all subjects are presented according to serum CA125 levels tertiles (Table 1). There were statistically significant differences between the 3 groups in age, BMI, TC, HDL-C, Cr, hs-CRP, diabetes mellitus, angiotensin-converting enzyme inhibitors, calcium ion channel blockers, and antidiabetic medications. Of note, the CAC score was found to be increased in the serum CA125 tertiles (31.6±82.10, 73.3±125.6, 122.9±135.9 U/mL, $p<0.001$) (Figure 1). The serum CA125 concentrations of the study population were grouped according to calcium-positive and calcium-negative, showing that serum CA125 concentrations are increased in calcium-positive patients compared to those who were calcium-negative (9.3±4.79 *vs.* 11.2±7.36, $p=0.003$), as shown in Figure 2. No significant differences were observed in other parameters, such as sex, ALT, AST, UN, GLU, TP, TG, LDL-C, hypertension, beta-blockers, and cholesterol-lowering therapy.

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Table 1. The clinical and laboratory characteristics of all subjects according to serum CA125 concentrations tertiles.

	I ≤6.5	II 6.5–11.7	III 11.7	p-Value
	N=114	N=117	N=117	
Gender (female/male)	74/40	62/55	60/57	0.076
Age(y)	53.9±14.51	57.3±14.89	59.2±14.92	0.015
Body mass index (Kg/m^2)	22.9±2.37	23.3±2.91	24.7±3.52	<0.001
Diabetes mellitus	16	27	56	<0.001
Hypertension	41	30	35	0.333
ACEI or ARB	40	36	2	<0.001
Beta- blockers	19	15	16	0.683
Ca channel blockers	19	10	27	0.010
Antidiabetics	31	26	56	<0.001
Cholesterol lowering therapy	11	8	17	0.148
Alanine transaminase (U/L)	16.9±7.32	17.6±7.45	17.8±7.11	0.626
Aspartate aminotransferase (U/L)	18.2±4.24	18.3±4.52	17.9±4.15	0.751
Total cholesterol (mmol/L)	4.3±1.00	4.3±1.13	4.0±1.00	0.024
Low density lipoprotein cholesterol (mmol/L)	2.7±0.85	2.8±1.01	2.5±0.85	0.051
High density lipoprotein cholesterol (mmol/L)	1.3±0.28	1.2±0.33	1.1±0.31	0.011
Triglycerides (mmol/L)	1.1±0.35	1.1±0.33	1.1±0.30	0.758
fasting blood glucose (mmol/L)	4.7±0.53	4.7±0.49	4.8±0.58	0.163
Total protein (g/L)	66.1±7.92	65.5±4.75	64.8±4.83	0.167
Creatinine (umol/L)	63.0±16.60	67.0±14.45	68.2±16.77	0.036
Urea nitrogen (mmol/L)	5.2±1.38	5.3±1.51	5.4±1.41	0.528
High-sensitivity C-reactive protein (mg/L)	1.2±0.95	1.3±1.02	3.1±2.65	<0.001
Coronary artery calcification score	31.6±82.10	73.3±125.6	122.9±135.9	<0.001

ACEI or ARB, Beta- blockers, Ca channel blockers and Antidiabetics mean medication use in different category.

The correlations between serum CA125 and age, BMI, BUN, HDL-C, TP, Cr, and hs-CRP (r=0.217, p<0.001; r=0.251, p<0.001; r=0.118, p=0.028; r=–0.185, p<0.001; r=–0.113, p=0.036, r=0.082, p=0.001; r=0.293, p<0.001) in all subjects. Interesting, we found a positive correlation between serum CA125 and CAC score (r=0.319, p<0.001) in all participants. Because serum CA125 levels differed in females and males, we divided all subjects into female and male for assessment of correlations. Serum CA125 concentrations were correlated with age, BMI, UN, Cr, and hs-CRP (r=0.232, p=0.001; r=0.328, p<0.001; r=0.142, p=0.018; r=0.120, p=0.045; r=0.229, p=0.001) in women, and were correlated with age, BMI, TP, and hs-CRP (r=0.180, p=0.026; r=0.188, p=0.020; r=–0.175, p=0.031; r=0.365, p<0.001) in men. Similarly, the serum concentrations of CA125 were positively correlated with CAC score in both women and men (r=0.328, p<0.001; r=0.265, p=0.001, respectively).

To control for major potential confounders that might influence the association between serum CA125 and CAC score in the study population, the multiple linear regression analysis used in this study, we used independent variables of sex, age, BMI, ALT, AST, LDL-C, HDL-C, TP, TG, Cr, hs-CRP, diabetes mellitus, hypertension, calcium ion channel blockers, beta-blockers, antidiabetic medications, and cholesterol-lowering therapy, and CAC score was considered as the dependent variable in multiple linear regression analysis. Our results indicated that serum CA125 concentrations were independently related to CAC score in the study population (beta=0.173, p=0.001), and age, sex, diabetes mellitus, and hs-CRP also

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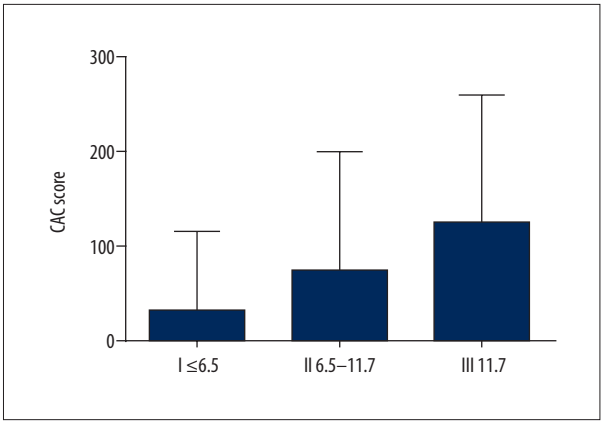

Figure 1. CAC score in study population according to the serum CA125 tertiles.

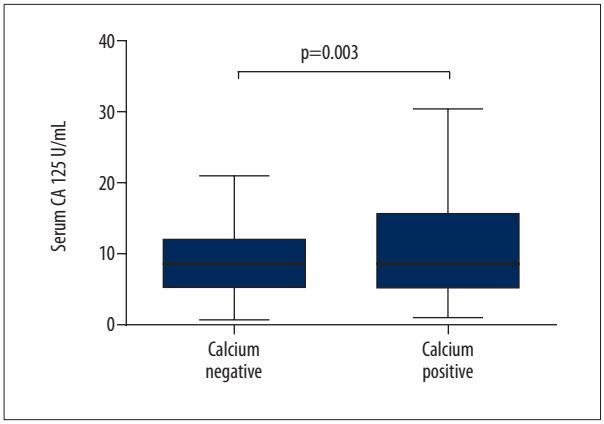

Figure 2. Serum CA125 concentrations of the study population were grouped as calcium-positive or calcium-negative.

Table 2. the relationship between serum CA125 and coronary artery calcification score in multivariable linear regression analysis.

	Unstandardized cofficients		Standardized cofficients	t	P-value
	B	Std Error	Beta		
Gender	31.180	10.482	0.126	2.915	0.003
age	3.434	0.375	0.411	9.549	<0.001
Diabetes mellitus	26.649	11.525	0.100	2.313	0.021
High-sensitivity C-reactive protein	12.661	3.166	0.198	3.999	<0.001
Serum CA125	3.160	0.916	0.173	3.450	0.001

were associated with CAC score in multiple linear regression analysis, as shown in Table 2.

Discussion

We found an independent relationship between increasing serum CA125 concentrations and CAC score after adjustment for multiple confounders in patients without known coronary artery disease, and serum hs-CRP concentrations were found to be associated with CAC score in multiple linear regression analysis.

CA-125 is secreted by the coelomic epithelial cells, including pericardium, peritoneum, pleura, and müllerian epithelium [16]. Higher serum concentrations of CA125 are linked with the presence of serous cavity effusion liver diseases and ovarian carcinoma [17, 18]. It has been reported that serum levels of CA125 are elevated in patients with heart transplantations [19]. Several studies have reported associations between serum CA125 and cardiovascular diseases [13, 14]. Our study revealed that increased CA125 levels are associated with CAC score in the study population. Although the mechanisms for elevated CA125 have not been elucidated, oxidative stress and inflammation may explain the relationship between serum CA125 with CAC score in our population. The secretion of serum CA125 is stimulated by mechanical stress and inflammation [20]. CAC deposition has been reported to be an indicator of overall plaque burden and future cardiovascular events [21]. Atherosclerotic plaques have inflammatory response and activity, and the appearance of calcifications is associated with atherosclerosis in the coronary arteries [22]. There are relationships between multiple classic markers of inflammation and CAC score in patients with and without cardiovascular disease, such as C-reactive protein, tumor necrosis factor, and interleukin-2 [23–25], and these inflammatory markers may be involved with the progression of CAC in the general population. In additional, vascular oxidative stress has been reported to be linked with atherosclerosis in humans with coronary artery disease [26,27], and the increased oxidative stress can promote and accelerate excessive intracellular calcium accumulation [28,29], which was associated with CAC scores in our study. Our study also found that serum CA125 is correlated with hs-CRP in the study population; the results agree that inflammation has an influence on serum CA125 concentrations. Thus, we can speculate that inflammation and oxidative stress may be a link in the relationship between serum CA125 and CAC scores in the study population.

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Some limitations should be noted in our study. First, patients with symptoms of chest pain were included to assess CAC score by CT scanning; therefore, the extrapolation of study results may be limited in other populations. Second, the determination of causality is not clear in the cross-sectional design. Third, the single-center measurement for all laboratory data may also be an inevitable limitation in the present study. Finally, a larger sample size with cohort study is needed.

Conclusions

The present data suggest that serum CA125 concentrations are correlated with CAC scores in the population without known coronary artery disease, and serum CA125 may be considered as a marker to estimate CAC in the study population.

Conflicts of interest

None.

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