

Original Article

Elevated carbohydrate antigen 242 and carbohydrate antigen 19-9 in lesion tissue is associated with gastric precancerous lesion

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Abstract: The study was to compare carbohydrate antigen (CA) 242 and CA19-9 in lesion tissue and serum, and explore the association with gastric precancerous lesions. Sixty-two patients were divided into gastric precancerous lesion group (32 patients with atrophic gastritis), and chronic superficial gastritis (CSG) group (30 patients with CSG). The gastric precancerous lesion group was further divided into moderate precancerous lesion (16 with atrophic gastritis and moderate gastric dysplasia) and severe precancerous lesion subgroups (16 with atrophic gastritis and severe gastric dysplasia). Serum and tissue samples were acquired from each patient. CA242 and CA19-9 levels in serum and tissue were measured by enzyme-linked immunoabsorbent assay and electro-chemiluminescence method, respectively. For the gastric precancerous lesion group, CA242 and CA19-9 in lesion tissue were significantly higher than those in serum ($P < 0.01$). Besides, CA242 and CA19-9 in lesion tissue were significantly increased in the gastric precancerous lesion group compared with the CSG group ($P < 0.01$). CA242 and CA19-9 in lesion tissue were significantly higher in severe precancerous lesion subgroup than those in moderate precancerous lesion subgroup ($P < 0.01$). However, no significant difference was detected in serum CA242 and CA19-9 between the two groups ($P > 0.05$). CA242 and CA19-9 in lesion tissue might aid in distinguishing gastric precancerous lesion from CSG, and is associated with gastric precancerous lesion severity.

Keywords: Gastric precancerous lesions, carbohydrate antigen, lesion tissue, chronic superficial gastritis, gastric dysplasia

Introduction

Gastric cancer (GC) is the third cause of cancer-related death worldwide and approximately accounts for 9% of deaths [1, 2]. The prognosis of patients with GC varies widely by cancer stage. The 5-year relative survival rate reaches up to 90% in early GC, but drops down to 5% in advanced GC cases [3]. Gastric precancerous lesion consists of chronic atrophic gastritis, intestinal metaplasia, and dysplasia. Dysplasia progresses from low grade to high grade [4, 5]. Since precancerous lesion is the pre-stage of GC, early detection of gastric precancerous lesion is of paramount importance to reduce the incidence of, and the mortality that results from, GC.

Measurement of serum biomarkers for gastric precancerous lesion has been regarded as an auxiliary approach to costly and invasive gas-

troscopic examination. A recent study shows that combination of serum pepsinogen II (PGII), and anti-*H. pylori* IgG may be a promising biomarker for assessment of development of gastric precancerous lesion [6]. Similarly, there is also evidence that serum PGI and PG I/II ratio may be useful to differentiate precancerous lesions from non-atrophic gastritis [7]. Besides, Serum carbohydrate antigens (CA) 242 is suggested to be a promising biomarker to differentiate GC from precancerous lesion in Chinese patients, but its positive rate is 79.2% [8]. Serum level of Carbohydrate antigens (CA) 19-9 is used to predict severity of gastric precancerous lesion with sensitivity of 63.28% and specificity of 63.2% in Chinese patients [9]. Despite considerable advancement, sensitivity and specificity of these identified serum biomarkers are inadequate for early detection of gastric precancerous lesion.

CA242 and CA19-9 indicative of gastric precancerous lesions

Table 1. Demographic data and history of patients in different groups

Variable	Gastric precancerous lesion group (n=32)	CSG group (n=30)	T/ χ^2	P-value
Mean age (year)	57.1±6.5	44.1±5.8	8.289	<0.001
Male/Female (n/%)	17/15 (53.1/46.9)	17/13 (56.7/43.3)	0.078	0.779
Disease history (n/%)			0.890	0.345
No other disease	12/37.5	15/50		
Hypertension and coronary heart disease	4/12.5	3/10		
Coronary heart disease	7/21.9	6/20		
Hypertension	6/18.8	4/13.2		
Diabetes	3/9.4	2/6.7		

CSG, Chronic superficial gastritis.

Although serum CA19-9 and CA242 has been proved to be useful in distinguishing GC from gastric precancerous lesion and associated with severity of gastric precancerous lesion, whether CA19-9 and CA242 in lesion tissue was associated with gastric precancerous lesion has not been unraveled. The present research compared CA19-9 and CA242 in lesion tissue and in serum. CA19-9 and CA242 in lesion tissue were extracted from obtained lesion tissue specimens by biopsy forceps from patients with gastric precancerous lesion or chronic superficial gastritis (CSG). We found that CA19-9 and CA242 in lesion tissue were remarkably elevated in gastric precancerous lesion than CSG. Moreover, levels of CA19-9 and CA242 in lesion tissue were related to severity of precancerous lesion.

Material and methods

Study population

The retrospective study enrolled 62 cases undergoing gastroscopy during the period from March 2013-June 2013 in the Fourth People's Hospital of Jinan city. The 62 patients were divided into 2 groups based on gastroscopy and histopathology-based diagnosis: gastric precancerous lesions group (n=32) and CSG (n=30) group. Demographic data of patients were displayed in **Table 1**. The gastric precancerous lesions group included 17 male and 15 female patients with an average age of 57.1±6.5 years old. Besides, the CSG group with an average age of 44.1±5.8 years old consisted of 17 male and 13 female patients. There was insignificant difference in male/female ratio between the two groups ($P>0.05$). But the CSG group was younger than the gas-

tric precancerous group ($P<0.001$). Past history was also collected from each patient (**Table 1**). As for the gastric precancerous lesion group, 12 patients were without any disease history; 4 with both hypertension and coronary heart disease history; 7 with only coronary heart disease history; 6 with only hypertension history; 3 with only diabetes history. In the CSG group, 15 patients were without any disease history; 3 with hypertension and coronary heart disease history; 6 with only coronary heart disease history; 4 with only hypertension history; 2 with only diabetes history. There was also insignificant difference in past history between the two groups ($P>0.05$).

Patients in the gastric precancerous lesions group (n=32) were diagnosed with chronic atrophic gastritis accompanied by moderate or severe gastric dysplasia, without presence of intestinal metaplasia. The CSG group (n=30) met the following criteria: CSG without gastric dysplasia or intestinal metaplasia. CSG, chronic atrophic gastritis, and gastric dysplasia were diagnosed by experienced doctors in Gastroenterology department based on histopathological analysis of experienced pathologists in our hospital in accordance with previous studies [10, 11].

The gastric precancerous lesions group was further divided into 2 subgroups: moderate precancerous lesion subgroup and severe precancerous lesion subgroup. The moderate precancerous lesion subgroup consisted of 16 patients with chronic atrophic gastritis and moderate gastric dysplasia, while the severe precancerous lesion subgroup included 16 patients presenting with chronic atrophic gastritis and severe gastric dysplasia. Gastric dys-

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Table 2. Measurement of CA242 and CA19-9 in lesion tissue and serum between Gastric precancerous lesion and GSG groups

Group	CA242		CA19-9	
	Tissue (ng/mL)	Serum (ng/ml)	Tissue (ng/mL)	Serum (ng/ml)
Gastric precancerous lesion group (n=32)	47.39±7.32* [#]	4.67±2.53	55.23±8.62* [#]	6.47±1.34
CSG group (n=30)	3.68±1.20	3.96±1.07	6.17±8.51	5.43±1.73

*P<0.01, significantly different in comparison with the serum level of CA242 or CA19-9 in gastric precancerous lesion group;

[#]P<0.01, significantly different in comparison with the level of CA242 or CA19-9 in tissue fluid in GSG group. CSG, chronic superficial gastritis. Analysis of covariance is used to adjust for age when comparing the difference in CA242 or CA19-9 between gastric precancerous lesion group and the CSG group.

plasia was graded by experienced pathologists in our hospital, in accordance with previous studies [10, 11]. Mild gastric dysplasia refers to cellular abnormality restricted to lower 1/3 of gastric epithelium thickness; Moderate gastric dysplasia, lower 1/3-2/3 of gastric epithelium thickness; severe gastric dysplasia, beyond lower 2/3 of gastric epithelium thickness without reaching full thickness. The study was approved by the ethnic committee of the Fourth People's Hospital of Jinan city. Patients with tumor or intestinal metaplasia or cardiopulmonary dysfunction were excluded from the survey. Written informed consent was acquired from each participant of the survey.

Samples collection

Before gastroscopy, serum sample was separated from 2 ml blood sample collected from each patient after an overnight fast for subsequent measurement of serum CA19-9 and CA242. During gastroscopy examination, patient was resting in left supine position. Disposable biopsy forceps with maximum diameter in 7 mm (Anrei Medical Company, Hangzhou, China) was utilized to obtain 4 specimens (diameter, 7 mm) from the lesion in the greater curvature of antrum. Two specimens were sent to the Pathology department for histopathological analysis. The other two specimens were digested and disassociated together in 1 ml 5% EDTA disodium solution for 24 h, and then subjected to centrifugation to extract supernatant for detection of CA242, CA19-9 in tissue.

Measurement of CA242 and CA19-9

CA242 in serum and lesion tissue was detected using enzyme-linked immuno-absorbent (ELISA) assay kit (CanAg, Sweden) by Multiskan

3 ELISA analyzer (Labsystems, Finland) and RT-2600c automatic microplate washer (Rayto, USA) [12]. The CA19-9 levels in serum and lesion tissue were measured by Electrochemiluminescence (ECL) method (Roche, Germany) [13]. Experimental procedures were conducted following the instructions.

Statistical analysis

SPSS11.5 software was used to calculate means and standard deviation (SD). The results were presented as means ± SD. Difference of each variable between two groups were examined by using Student's test or Chi-square test as appropriate. Analysis of covariance was used to adjust for potential confounders. The 95% confidence interval for the mean values of CA242 and CA19-9 in lesion tissue in the control group was defined as normal values.

Results

Comparison of CA242 and CA19-9 between gastric precancerous lesion and CSG groups

CA242 and CA19-9 in lesion tissue and serum were measured and compared in gastric precancerous lesion and CSG groups. As shown in **Table 2**, for gastric precancerous lesion group, both CA242 and CA19-9 were significantly increased in tissue than those in serum ($P<0.01$), whereas CSG group had no significance in CA242 and CA19-9 between tissue and serum ($P>0.05$).

Because age was significantly different between the CSG group and the gastric precancerous group (44.1±5.8 years vs 57.1±6.5 years; $P<0.05$), analysis of covariance was used to adjust for age when comparing the dif-

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Table 3. Comparison of CA242 and CA19-9 in serum and lesion tissue between severe and moderate precancerous lesion subgroups

Subgroups	CA242		CA19-9	
	Tissue (ng/mL)	Serum (ng/ml)	Tissue (ng/mL)	Serum (ng/ml)
Severe precancerous lesion (n=16)	57.63±12.87*	5.82±1.39	61.37±10.52*	5.98±1.64
Moderate precancerous lesion (n=16)	32.42±8.51	5.16±1.54	42.81±7.63	5.43±1.27

*Significantly different compared with the level of CA242 or CA19-9 in tissue fluid in the moderate precancerous lesion subgroup, $P < 0.01$.

ferences in CA242 and CA19-9 between the two groups. There was no difference in serum CA242 and CA19-9 between gastric precancerous lesion and CSG groups ($P > 0.05$, **Table 2**). However, both CA242 and CA19-9 in lesion tissue were remarkably increased in gastric precancerous lesion group compared to those in the CSG group ($P < 0.01$, **Table 2**). It suggested that CA242 and CA19-9 in tissue, rather than in serum might be useful to differentiate gastric precancerous lesion from CSG.

Comparison of CA242 and CA19-9 between severe and moderate precancerous lesion subgroups

In order to determine whether the levels of CA242 and CA19-9 was associated with severity of precancerous lesion, CA242 and CA19-9 in serum and lesion tissue were also measured in moderate and severe precancerous lesion subgroups. As shown in **Table 3**, there was insignificant difference in serum CA19-9 and CA242 between severe and moderate precancerous lesion subgroups ($P > 0.05$). Nevertheless, severe precancerous lesion group had markedly higher level of CA242 and CA19-9 in lesion tissue than moderate precancerous lesion group ($P < 0.01$). It indicated that CA242 and CA19-9 in tissue was associated with the progression grade of precancerous lesion.

Discussion

Management of gastric precancerous lesion is critical for prevention of GC around the world. Regular serum markers only serve as a supplement to gastroscopy screening. The current study compared CA242 and CA19-9 in lesion tissue and serum, and explored whether they were associated with gastric precancerous lesion. Because either chronic superficial or

atrophicgastritis is diffuse lesion, and typically occurs at the greater curvature of antrum. We obtained specimens from this position to compare the changes between patients. Results of the study showed that CA242 and CA19-9 level in lesion tissue appeared to be higher than those in serum for patients with gastric precancerous lesion.

CA19-9, a type of Tumor-associated carbohydrate antigens (TACAs), is a product of gene *Lewis*. It has long been reported that serum CA19-9 is associated with GC prognosis and recurrence [14-16]. Similarly, serum CA242 is significantly higher in GC than that in control groups and recognized as an independent prognostic marker in GC patients [17]. Although CA19-9 and CA242A are recommended as serum biomarkers to differentiate gastric precancerous lesion from GC or predict the progression grade of gastric precancerous lesion, their sensitivities are limited in Chinese patients [8, 9]. In agreement with these reports, the present study found serum CA19-9 and CA242 were insignificantly higher between gastric precancerous lesion group and CSG group. These findings further confirmed that measurement of serum CA242 and CA19-9 only was insufficient for detection of gastric precancerous lesion. In contrast, CA19-9 and CA242 in lesion tissue were considerably higher in gastric precancerous lesion group than that in the CSG group. We could speculate that CA19-9 and CA242 in lesion tissue might be more sensitive to the neoplastic transformation of gastric cell than those in serum.

Gastric cancerogenesis is a complicated stepwise process, progressing from acute gastritis to chronic gastritis, intestinal metaplasia, dysplasia and adenocarcinoma in a sequence. It has been established that precancerous lesions often precede gastric malignancy and increase malignancy risk [18, 19]. Follow-up

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data reveals no discrepancy in clinical manifestations between precancerous lesions and GC [20, 21]. Therefore, to track precancerous lesions is very crucial for GC prevention. Nevertheless, serological markers CA19-9 and CA242 are not sensitive or specific enough to detect patients at high risk of precancerous lesions [22, 23]. Hopefully, in the present study, CA242 and CA19-9 in lesion tissue was significantly increased in severe precancerous lesion subgroup than that in moderate precancerous lesion subgroup. However, no significant difference was observed in serum CA242 and CA19-9 levels between the two groups. These findings suggested that CA242 and CA19-9 in lesion tissue might be promising biomarkers in distinguishing gastric precancerous lesion from CSG, and distinguishing moderate gastric dysplasia from severe gastric dysplasia.

Application of novel endoscopic techniques has been introduced into regular examinations in Japan due to its high sensitivity so as to improve the detection rate of early GC. In the United States, endoscopic resection of high-grade dysplasia is also encouraged as an alternative to surgical intervention [23]. Although gastroscopy with biopsy forceps is an invasive approach, it is an easy and operable method to measure CA242 and CA19-9 in lesion tissue, which is more sensitive than conventional serological tumor markers.

It is a preliminary study and has limitations. First, only 62 cases participated in the current study. Inevitably, the small sample size limits the power of the study. We need to validate the result of the study, and to recapitulate the specificity and sensitivity of CA242 and CA19-9 in lesion tissue in a large population in clinical practice. Second, it is an invasive procedure. Third, histological analysis could also be made followed by gastroscopic biopsy. That meant that CA242 and CA19-9 in tissue could be used as a supplementary measure to histological examination. However, our study provides useful information regarding the levels of CA242 and CA19-9 in lesion tissue to predict precancerous lesion. Based on previous experience of clinical laboratory of our hospital, the normal value of CA242 in lesion tissue was determined to be <4.18 ng/ml; CA19-9 in lesion tissue,

<9.65 ng/ml; normal values of CA242 and CA19-9 in serum were 0-20 ng/ml, and 0-27 ng/ml, respectively. Furthermore, detection of CA242 and CA19-9 in tissue is more convenient and less costly than histological examination.

Collectively, CA19-9 and CA242 in lesion tissue might aid in distinguishing gastric precancerous lesion from CSG, and is associated with precancerous lesion severity. CA242 and CA19-9 expression in lesion tissue might be recommended as better markers than serum markers for early detection of gastric precancerous lesion in clinical practice, thus reducing the incidence of GC. More studies are warranted to validate the findings of this study.

Disclosure of conflict of interest

None.

Authors' contribution

Haiyan Wang participated in the design of this study, performed the statistical analysis and drafted the manuscript.

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