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Correlations of serum homocysteine, VEGF and gastrin 17 with gastric cancer and precancerous lesions

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Abstract. – OBJECTIVE: To investigate the correlations of Homocysteine (Hcy), vascular endothelial growth factor (VEGF), and serum gastrin 17 (G17) with gastric cancer and precancerous lesions.

PATIENTS AND METHODS: A total of 56 patients with gastric cancer (gastric cancer group) and 53 patients with precancerous lesions (precancerous lesion group) admitted to Heze Municipal Hospital from January 2017 to October 2018 were selected, and 50 healthy subjects undergoing the physical examination in the same period were selected as control group. The levels of serum Hcy, VEGF, and G17 in the three groups were compared, and the relations of each index with clinicopathological characteristics of gastric cancer were analyzed.

RESULTS: The levels of serum Hcy, VEGF-A, VEGF-C, VEGF-D, and G17 in gastric cancer group and precancerous lesion group were higher than in control group, and those in gastric cancer group were higher than in precancerous lesion group ($p<0.05$). Besides, the high expression levels of serum Hcy, VEGF, and G17 had evident correlations with the tumor-node-metastasis (TNM) stage, Lauren type, infiltration depth, and lymph node metastasis of gastric cancer ($p<0.05$).

CONCLUSIONS: Hcy, VEGF, and G17 can exhibit different levels of expressions in precancerous lesions. They are also highly expressed in gastric cancer. Besides, they are involved in the occurrence and development of gastric cancer and can be regarded as crucial indexes with clinical significance for the differential diagnosis of gastric cancer and precancerous lesions in the early stage.

Key Words:
Hcy, VEGF, Gastrin 17, Gastric cancer, Precancerous lesion.

Introduction

Gastric cancer is a common malignant tumor of the digestive tract in clinic and it changes with people's diet structure, whose incidence rate shows an increasing trend year by year. Moreover, gastric cancer, with its incidence and mortality rates ranking top three among malignant tumors, poses a serious threat to human life and health[1,2]. Gastric cancer results from progressive development involving multiple steps and factors. It is difficult to make early diagnosis due to small foci, inconspicuous symptoms, and poor health care consciousness of most patients, which often used to be at advanced stage with a generally poor prognosis when diagnosed[3]. Therefore, early screening, diagnosis, and treatment are important measures to reduce its incidence rate. Clinically, the individual screening for gastric cancer is dominated by endoscopic examination, which is an invasive treatment with high costs and poor compliance of patients. Hence, finding a suitable, simple and non-invasive primary screening method is very crucial. Homocysteine (Hcy) is a sulfur-containing amino acid with a close correlation with cell carcinogenesis[4]. The vascular endothelial growth factor (VEGF), as a cell regulatory factor that affects the blood vessel formation and growth of tumors, is closely related to the occurrence of tumors[5]. Serum gastrin 17 (G17) is one of the gastric mucosa serological biopsy indexes, which is valuable in screening gastric diseases[6]. In this study, the expression levels of serum Hcy, VEGF, and G17 in gastric cancer and precancerous lesions were detected, and their correlations with gastric diseases were analyzed to provide a basis for gastric cancer screening and early diagnosis.

Patients and Methods

Patients

A total of 56 patients with gastric cancer (gastric cancer group) and 53 patients with precancerous lesions (precancerous lesion group) admitted

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to Heze Municipal Hospital from January 2017 to October 2018 were selected, and 50 healthy subjects receiving the physical examination were selected as control group. In gastric cancer group, 38 cases were male and 18 cases were female, the average age was 34-71 with an average pf (50.13±4.56) years old. The tumor-node-metastasis (TNM) staging included 16 cases of stage I, 15 cases of stage II, 13 cases of stage III, and 12 cases of stage IV. About Lauren typing, 26 cases of diffuse type and 30 cases of intestinal type; 20 cases of submucosal invasion, 13 cases of muscular layer invasion, and 23 cases of serous layer invasion. There were 32 cases with lymph node metastasis and 24 cases without lymph node metastasis. There were 36 males and 17 females with (49.58 ±3.21) years old in precancerous lesion group. In control group, there were 35 males and 15 females, aged 35 to 70 years with a mean age of (48.69 ±3.07) years old.

Inclusion criteria for gastric cancer patients: 1) patients with the disease meeting the diagnosis criteria for gastric cancer and confirmed by pathology and imaging[7]; 2) patients with more than 3 months of expected survival period receiving no operation, radiotherapy and chemotherapy; 3) patients who signed the informed consent with their family members.

Exclusion criteria: 1) patients with dysfunction of the heart, liver, kidney, lung or blood system; 2) patients with mental diseases; 3) patients with a history of high Hcy genetic disease; 4) patients complicated with other tumors. All experimental subjects who had received drug therapy within one month that might cause an increase in Hcy level were excluded. There were no statistical differences in baseline data among the three groups (p>0.05).

Methods

A total of 5 mL fasting venous blood was collected from all subjects and centrifuged at 5000 r/min for 15 min using a centrifuge (Changsha Weierkang Xiangying Centrifuge Co., Ltd., Hunan, China). Then, serum was extracted and stored at –70°C.

The concentration level of VEGF was detected by the enzyme-linked immunosorbent assay (ELISA) according to the instructions of related kits provided by RB Rapid Bio (Minneapolis, MN, USA). Specific steps: the standard sample was diluted and added in the well (blank, sample to be tested), then incubated at 37°C for 30 min, washed for 5 times and incubated with the enzyme at 37°C for 30 min. Next, it was washed for 5 times and the dry color was beaten and the determination was stopped. The OD value was read at 450 nm with a microplate reader (Awareness, Bellport, NY, USA), and the concentrations of VEGF-A, VEGF-C, and VEGF-D were calculated. The steps and results calculation were the same as in the determination of VEGF.

Subsequently, the serum Hcy level was measured by the circulating enzyme assay using the 7600-120DPP modular large-scale full-automatic biochemical analyzer (Hitachi, Tokio, Japan) in strict accordance with the instructions of the related reagents (Beijing Jiuqiang Biotechnology Co., Ltd, Beijing, China). The principle was based on small molecular capture technique (SMT) of S-adenosine homocysteine detection. The reaction conditions were as follows: 37°C at the main wavelength of 340 nm and a secondary wavelength of 405 nm. The optical path of the colorimetric cup was 1 cm. Subsequently, the G17 level was strictly detected via ELISA based on the instructions of related kits (Biohit, Helsinki, Finland).

Evaluation Criteria

According to the depth of tumor invasion, tumor-node-metastasis (TNM) stages of gastric cancer were classified[8] into Tis (tumor cells were located in the mucosal layer), T_1 (tumor cells were located in the submucosa and mucosa), T_2 (tumor cells infiltrated into the serosal layer or muscular layer), T_3 (tumor cells penetrated the serosal layer), and T_4 (tumor cells expanded into the duodenum and esophagus in the cavity or invaded into adjacent tissue structures). At least 15 lymph nodes in specimens were taken out for pathological analysis to confirm the lymph node metastasis status, based on which the TNM stages of gastric cancer were classified into N_0 (no lymph node metastasis), N_1 (regional metastasis occurred in 1-6 lymph nodes), N_2 (regional metastasis occurred in 7-15 lymph nodes), and N_3 (regional metastasis occurred in more than 15 lymph nodes). According to the status of distant metastasis confirmed by pathology, TNM stages of gastric cancer were classified into M_0 (no distant metastasis) and M_1 (distant metastasis occurred in the abdominal aorta, mesentery, and pancreatic posterior lymph nodes). Specifically, TNM stages could be divided into 1) stage I: $T_{is}N_0M_0$, $T_1N_0M_0$, $T_2N_0M_0$, $T_1N_1M_0$, 2) stage II: $T_1N_2M_0$, $T_2N_1M_0$, $T_{is}N_1M_0$, $T_{is}N_0M_0$, $T_3N_0M_0$, 3) stage III: $T_2N_2M_0$, $T_3N_1M_0$, $T_3N_1M_0$, $T_4N_0M_0$, and 4) stage IV: $T_4N_{1\text{-}3}M_0$, $T_{1\text{-}3}N_3M_0$, $T_{is\text{-}4}N_{0\text{-}3}M_0$.

Table I. Serum levels of Hcy and G17 in the three groups.

Group	No.	Hcy (μmol/L)	G17 (pmol/L)
Gastric cancer group	56	18.23±2.03	6.97±0.73
Precancerous lesion group	53	9.54±1.56	4.59±0.47
Control group	50	6.13±1.07	3.25±0.42
F		19.685	12.533
p		<0.001	<0.001

Statistical Analysis

SPSS 19.0 software (SPSS Inc., IBM, Armonk, NY, USA) was used for data processing. Measurement data were expressed as mean ± standard deviation ($\chi \pm s$) and detected via the *t*-test. Comparisons of data among multiple groups were examined via the F test. Count data were expressed as a percentage and detected using the χ^2-test. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of the Levels of Serum Hcy and G17 Among the Three Groups

The serum levels of Hcy and G17 in gastric cancer group and precancerous lesion group were higher than in control group, and those in gastric cancer group were higher than in precancerous lesion group ($p<0.05$) (Table I).

Comparisons of the Serum VEGF Level Among the Three Groups

Gastric cancer group and precancerous lesion group had higher levels of serum VEGF-A, VEGF-C, and VEGF-D than control group and those in gastric cancer group were higher than in precancerous lesion group ($p<0.05$) (Table II).

Relationship Between the Serum Hcy Expression and Clinicopathology of Gastric Cancer

The high expression level of Hcy was notably correlated with the TNM stage, Lauren type, infiltration depth, and lymph node metastasis of gastric cancer ($p<0.05$). Patients with diffuse cancer, higher TNM stage, infiltration into the serosal layer, and lymph node metastasis had a higher Hcy level than those with intestinal cancer, lower TNM stage, no infiltration into the serosal layer, and no lymph node metastasis ($p<0.05$) (Table III).

Relationship Between the Serum VEGF Expression and Clinicopathology of Gastric Cancer

The high expression levels of VEGF-A, VEGF-C, and VEGF-D had evident correlations with the TNM stage, Lauren type, infiltration depth, and lymph node metastasis of gastric cancer ($p<0.05$). Patients with diffuse cancer, higher TNM stage, infiltration into the serosal layer, and lymph node metastasis had higher expression levels of VEGF-A, VEGF-C, and VEGF-D than those with intestinal cancer, lower TNM stage, no infiltration into the serosal layer and no lymph node metastasis ($p<0.05$) (Tables IV-VI).

Relationship Between the Serum G17 Expression and Clinicopathology of Gastric Cancer

The high expression level of G17 had an evident correlation with the TNM stage, Lauren type, infiltration depth and lymph node metastasis of gastric cancer ($p<0.05$). The expression level of G17 in patients with diffuse cancer, higher TNM stage, infiltration into the serosal layer and lymph node metastasis was higher than that in

Table II. Serum VEGF level in the three groups.

Group	No.	VEGF-A (pg/mL)	VEGF-C (pg/mL)	VEGF-D (pg/mL)
Gastric cancer group	56	129.64±9.78	1936.48±116.65	1636.45±113.73
Precancerous lesion group	53	79.72±6.53	834.62±85.46	714.58±72.53
Control group	50	56.13±5.16	483.16±52.38	423.37±51.46
F		35.168	89.267	87.516
p		<0.001	<0.001	<0.001

Table III. Relationship between the Hcy expression and clinicopathology of gastric cancer.

Item	No.	Hcy (μmol/L)	t/F	p
TNM stage			32.536	<0.001
Stage I	16	13.18±1.53		
Stage II	15	15.85±1.16		
Stage III	13	23.73±2.35		
Stage IV	12	29.62±2.76		
Lauren type			10.533	<0.001
Diffuse type	26	19.64±2.78		
Intestinal type	30	14.57±2.13		
Depth of infiltration			29.533	<0.001
Submucosal layer	20	14.63±2.03		
Muscular layer	13	20.62±2.17		
Serosal layer	23	28.14±2.82		
Lymph node metastasis			22.372	<0.001
Yes	32	26.52±2.63		
No	24	13.12±1.85		

patients with intestinal cancer, lower TNM stage, no infiltration into the serosal layer and no lymph node metastasis ($p<0.05$) (Table VII).

Discussion

As the most common malignant tumor clinically, gastric cancer results from multi-step and progressive development with a very complex etiology and pathogenesis. It evolves from superficial gastritis, atrophic gastritis, and dysplasia into different stages[9,10]. Diet, environment, *Helicobacter Pylori* infection, precancerous lesion, and genetic factors damage human cell DNAs. Gene damage will accumulate continuously in case the damage cannot be timely repaired, resulting in abnormal proliferation or apoptosis of cells and eventually triggering gastric cancer[11]. In the early stage, gastric cancer is mainly manifested with common symptoms such as nausea and vomiting without typical symptoms, so it is very difficult to be cured in the early stage, and once definitely diagnosed, most patients are in the advanced stage[12]. Therefore, improving screening and early diagnosis is of great significance to reduce the mortality rate and prolong the survival time of patients. Hcy is a sulfur-containing amino acid synthesized by demethylation of methionine

Table IV. Relationship between the VEGF-A expression and clinicopathology of gastric cancer.

Item	No.	Hcy (μmol/L)	t/F	p
TNM stage			42.765	<0.001
Stage I	16	61.64±5.78		
Stage II	15	82.75±6.57		
Stage III	13	135.64±9.82		
Stage IV	12	169.53±11.46		
Lauren type			29.191	<0.001
Diffuse type	26	139.63±10.65		
Intestinal type	30	68.62±6.83		
Depth of infiltration			43.643	<0.001
Submucosal layer	20	62.62±5.43		
Muscular layer	13	93.57±7.25		
Serosal layer	23	168.54±11.86		
Lymph node metastasis			45.164	<0.001
Yes	32	169.57±11.68		
No	24	62.35±5.74		

Table V. Relationship between the VEGF-C expression and clinicopathology of gastric cancer.

Item	No.	VEGF-C (pg/mL)	t/F	p
TNM stage			78.145	<0.001
Stage I	16	578.29±61.54		
Stage II	15	1265.85±79.14		
Stage III	13	1983.73±126.37		
Stage IV	12	2139.65±138.74		
Lauren type			45.514	<0.001
Diffuse type	26	2035.62±132.65		
Intestinal type	30	684.87±78.23		
Depth of infiltration			68.478	<0.001
Submucosal layer	20	576.48±56.38		
Muscular layer	13	1134.28±115.46		
Serosal layer	23	2163.16±142.37		
Lymph node metastasis			57.166	<0.001
Yes	32	2126.58±135.62		
No	24	583.15±60.83		

in protein foods. It will produce certain toxicity in the processes of formation and metabolism and has a close correlation with cancerous lesions of cells[13]. According to the results of this study, the level of serum Hcy in gastric cancer group and precancerous lesion group was higher than in control group, and that in gastric cancer group was higher than that in precancerous lesion group. The high expression level of serum Hcy was markedly correlated with the TNM stage, Lauren type, infiltration depth, and lymph node metastasis of gastric cancer ($p<0.05$). This is probably due to the fact that Hcy will reduce the expression of tumor suppressor genes in the process of metabolism. It will also promote the continuous growth and proliferation of gastric tumor cells, producing related substances with oxidative damage, thus leading to the accumulation of Hcy in blood, affecting the vascular endothelium, promoting cell division and proliferation, promoting the angiogenesis, and influencing the infiltration and metastasis of the tumor. VEGF, the most active angiogenic factor in the platelet-derived growth factor family, includes VEGF-A, VEGF-C, and VEGF-D. VEGF exhibits high expression in the serum of many tumor patients and is closely related to the pathological grade of malignant tumors[14]. VEGF-A is capable of promoting the division and proliferation of vascular endothelial cells, as well

Table VI. Relationship between VEGF-D expression and clinicopathology of gastric cancer.

Item	No.	VEGF-D (pg/mL)	t/F	p
TNM stage			89.178	<0.001
Stage I	16	513.17±47.54		
Stage II	15	1115.85±103.15		
Stage III	13	1723.36±122.34		
Stage IV	12	2029.63±132.86		
Lauren type			56.239	<0.001
Diffuse type	26	1987.64±123.78		
Intestinal type	30	524.58±51.23		
Depth of infiltration			82.136	<0.001
Submucosal layer	20	536.47±43.72		
Muscular layer	13	814.42±72.53		
Serosal layer	23	1923.57±121.46		
Lymph node metastasis			62.601	<0.001
Yes	32	2026.58±122.68		
No	24	518.32±51.42		

Table VII. Correlation between the G17 expression and clinicopathology of gastric cancer.

Item	No.	G17 (pmol/L)	*t/F*	*p*
TNM stage			26.138	<0.001
Stage I	16	3.78±0.53		
Stage II	15	4.15±0.66		
Stage III	13	7.23±0.85		
Stage IV	12	8.62±0.76		
Lauren type			24.562	<0.001
Diffuse type	26	8.34±0.78		
Intestinal type	30	3.87±0.54		
Depth of infiltration			21.547	<0.001
Submucosal layer	20	3.97±0.53		
Muscular layer	13	4.89±0.67		
Serosal layer	23	8.25±0.72		
Lymph node metastasis			28.162	<0.001
Yes	32	8.82±0.83		
No	24	3.72±0.52		

as neovascularization[15,16]. VEGF-C and VEGF-D can stimulate lymphangiogenesis and tumor lymphatic metastasis[7]. It was found from the results of this study that the levels of serum VEGF-A, VEGF-C, and VEGF-D in gastric cancer group and precancerous lesion group were higher than in control group, and those in gastric cancer group were higher than in precancerous lesion group. The high expression levels of serum VEGF-A, VEGF-C, and VEGF-D were prominently correlated with the TNM stage, Lauren type, infiltration depth, and lymph node metastasis of gastric cancer (p<0.05). The reason may be that VEGF-A, as a vascular growth factor with the highest specificity, induces the mitosis of cells and accelerates the differentiation of endothelial cells to cause the generation of a large number of new vessels in patients, thus leading to a deeper infiltration. In the meantime, VEGF-A also enhances the formation and growth of lymphatics in patients and maintains the integrity of its structure and function, thereby promoting the metastasis and invasion of tumor cells[17]. VEGF-C and VEGF-D expand the lymphatics of patients, increase their permeability, expand the contact area between lymphatics and surrounding tumor cells, raise the probability of tumor cells transferring through lymphatics, and accelerate the fusion of new lymphatics with blood vessels, resulting in systemic metastasis of tumor cells[18].

G17 is a peptide hormone that affects gastric parietal cells via blood circulation, stimulates gastric acid secretion, and plays vital roles in the structural and functional integrity of the digestive system[19]. Relevant studies[20] have verified that G17 exerts a crucial effect during the occurrence and development of gastric cancer. The results of this work showed that gastric cancer group and precancerous lesion group had a higher G17 level in serum than control group, and the level of serum G17 in gastric cancer group was higher than that in precancerous lesion group. Besides, the high expression level of serum G17 was significantly related to the TNM stage, Lauren type, infiltration depth, and lymph node metastasis of gastric cancer (p<0.05). The reason may be that G17 induces acid secretion, aggravates gastric mucosa damage and promotes tumor occurrence. Moreover, G17 can be combined with the receptor on the gastric mucosal cell surface to activate the JAK/STAT3/PI3K/Akt signaling pathway, thereby boosting the proliferation and malignant transformation of tumor cells. Meanwhile, G17 is able to activate the JNK1 and MLK3 signaling pathways to induce the activation of matrix metalloproteinases, thus degrading the extracellular matrix, deepening tumor cell infiltration, leading to distant metastasis and aggravating lymph node metastasis.

Conclusions

We showed that Hcy, VEGF, and G17 can be used as pivotal indicators for differentially diagnosing gastric cancer and precancerous lesions, as well as for the occurrence and development of gastric cancer. Also, they are of certain guiding significance for the diagnosis and treatment of patients.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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