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ORIGINAL ARTICLE

Expression and clinical significance of serum lipoprotein (a) in patients with gastric cancer

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Abstract

Objective This study aimed to investigate the expression and clinical significance of serum lipoprotein (a) [LP (a)] in patients with gastric cancer.

Methods Two hundred and twenty-two patients with gastric cancer (gastric cancer group) were selected from 2015 to 2017 [mean age (58.40 ± 10.40) years], as were 101 healthy persons [normal age group, mean age (58.18 ± 11.42) years]. Fasting blood samples were collected and evaluated by immunoturbidimetry with a biochemical analyzer. LP (a) concentration was observed and its difference was compared.

Results There was no significant correlation between LP (a) and tumor stage ($P > 0.05$). Compared with the control group, the level of LP (a) in the male gastric cancer group was significantly higher than that in the control group ($P < 0.05$). In the subgroup analysis, the level of LP (a) and abnormal rate showed an increasing trend among patients with stages I–IV gastric cancer. The level of LP (a) in poorly differentiated gastric cancer patients was higher than that in the high middle differentiation group ($P < 0.05$). There was no significant difference in LP (a) levels among patients with different pathological types of gastric cancer ($P > 0.05$).

Conclusion LP (a) was correlated with the occurrence, development and differentiation of gastric cancer, but not with the pathological classification of gastric cancer. Serum LP (a) concentration may be used as an indicator for the staging and prognosis of gastric cancer, but the specific underlying mechanism remains to be further studied.

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Key words: lipoprotein (a) [LP (a)]; gastric cancer; staging; differentiation; pathological typing

In February 2017, the National Cancer Center released the latest cancer data for China, with about 10 000 people diagnosed with cancer every day. Gastric cancer is one of the most common malignant tumors. The incidence of gastric cancer is increasing year by year, ranking first in the incidence of gastrointestinal malignant tumors, and the mortality rate ranks second in the total mortality rate of cancer. Early detection and treatment of gastric cancer is key. The expression and clinical significance of lipoprotein (a) [LP (a)] in gastric cancer patients are discussed in this paper.

LP (a), discovered and named by the Norwegian geneticist Kåre Berg in 1963, is a complex and independent plasma lipoprotein. Apolipoprotein (a) (apo A) binds to low-density lipoprotein (LDL) via disulfide bonds, but its physical and chemical properties are essentially different from LDL [1]. It is relatively stable in individual expression and is not subject to dietary habits and geographical differences among the same races. However, LP (a) levels are largely dependent on genes, so there may be great differences between different races. Conventional studies have shown that [2–4] LP (a) increases the risk of cardiovascular disease because of its thrombotic and atherosclerotic properties. Interestingly, serum LP (a) levels were negatively correlated with levels of vascular endothelial growth factor and coronary collateral circulation development in patients with coronary heart disease. In recent years, many oncology experts [5–6] have focused on the possible role of LP (a) in tumor angiogenesis and development, and found that LP (a) has a significant impact on tumor expansion and metastasis. A small sample of data has shown that increased concentration of LP (a) increases the risk of certain cancers and affects their staging (such as breast cancer and acute myeloid leukemia). Up till now, no studies have discussed the relationship between LP (a)

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levels and the occurrence, development, staging and differentiation of gastric cancer. The aim of this study was to investigate the expression and clinical significance of LP (a) level in gastric cancer patients [7–13].

Data and methods

General information

Two hundred and twenty-two patients, 152 male and 70 female, who were diagnosed as primary gastric cancer by histopathology, aged 18–75 years, Eastern Cooperative Oncology Group (ECOG) performance status 1–2, and of Han nationality, were retrospectively enrolled in our hospital (Affiliated Hospital of Qingdao University, China) from 2015 to 2017. The inclusion criteria were body mass index (BMI) 17.9–23.9 kg/m^2, no clinical evidence of vascular disease (such as coronary artery disease, stroke, peripheral artery disease), no active inflammatory disease, and no history of drug use affecting lipid metabolism and coagulation function within 3 months. The exclusion criteria were abnormal lipid metabolism, BMI < 17.9 kg/m^2 or > 23.9 kg/m^2; clinically significant vascular disease (coronary heart disease, stroke, peripheral artery disease); abnormal liver function (transaminase and/or gamma-glutamyltransferase increased 2.5 times the upper limit of normal or clinical jaundice; abnormal renal function (creatinine or urea nitrogen concentration increased 1.5 times the upper limit of normal); coagulation system dysfunction (increased fibrin 2 times the upper limit of normal or D-dimer > 800 ng/mL); and application of drugs affecting lipid metabolism and coagulation function within the preceding 3 months. One hundred and one age-matched healthy persons undergoing check-up were included in the same period.

Data acquisition and evaluation criteria

Pathological analysis and grading of biopsy specimens were performed via endoscopic examination, laparoscopic resection and laparotomy. Ultrasound, computed tomography, magnetic resonance imaging, and bone scan were used to confirm the histological classification of gastric cancer, including adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma. All patients with carcinoma *in situ,* stage I, stage II, stage III, and stage IV were identified according to the staging system of the 2007 V1 National Comprehensive Cancer Network guidelines. Serum LP (a) concentration was measured in the fasting state by the immunoturbidimetric method.

Statistical analysis

SPSS version 22 (IBM Corp., Armonk, NY, USA) was used to analyze the data. The measurement data were skewed on the normality test, and the classified variables were expressed as frequencies and percentages. The comparison between groups was performed by analysis of variance, and rates were compared using the chi-square test. The correlation between serum LP (a) and tumor staging was evaluated using the independent samples *t*-test. Differences were statistically significant at $P < 0.05$.

Results

There was no statistically significant difference in the concentration of LP (a) between the gastric cancer group and control group ($P > 0.05$). The differences in LP (a) between the gastric cancer group and control group and between different stages are compared in Fig. 1.

The concentration of LP (a) in male patients with gastric cancer [mean: (325.56 ± 279.06) mg/L] was compared with that in the control group [mean: (169.08 ± 8.56) mg/L] ($P = 0.000$). Subgroup analysis of different stages showed that stage 0 [mean: (116.50 ± 23.39) mg/L] and stage I [mean: (127.82 ± 6.92) mg/L] had higher values than those of stage II [mean: (149.04 ± 10.53) mg/L] ($P = 0.094$); stage II was compared with stage III [mean: (405.30 ± 36.62) mg/L] ($P = 0.000$), stage III was compared with stage IV [mean: (469.07 ± 49.60) mg/L] ($P = 0.298$), and stage IV was compared with the healthy control group ($P = 0.000$). The relationship between LP (a) and the depth of tumor invasion, local lymph node metastasis, nerve invasion, vascular tumor embolism, and *HER-2* expression were also investigated. The results showed that LP (a) level was positively correlated with neurological invasion and vascular tumor thrombus channel positive, and LP (a) level was $P < 0.05$ in the comparison of positive and negative neurological invasion and vascular invasion, while the depth of tumor invasion was deep, local lymph node metastasis $P > 0.05$. The clinical characteristics of male patients with gastric cancer and male health examiners are shown in Table 1. The differences in LP (a) levels between male patients with gastric cancer and male health examiners and between different stages were compared as shown in Fig. 2.

LP (a) levels in male patients with poorly differentiated gastric cancer [mean: (342.86 ± 26.01) mg/L] were significantly higher than those in patients with high-moderately differentiated gastric cancer [mean: (237.68 ± 34.26) mg/L] ($P = 0.018$). The differences in LP (a) level between the gastric cancer groups according to different degrees of differentiation are shown in Fig. 3.

There was no significant difference in LP (a) levels among patients with gastric adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma ($P > 0.05$). The differences in LP (a) concentration between different pathological types of gastric cancer are shown in Fig. 4.

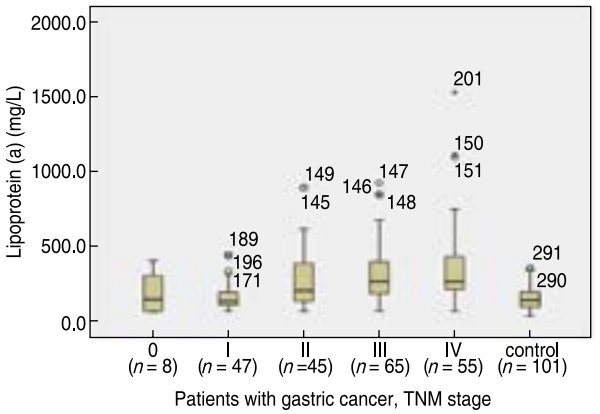

Fig. 1 Differences in lipoprotein (a) level among patients with gastric cancer according to TNM stage

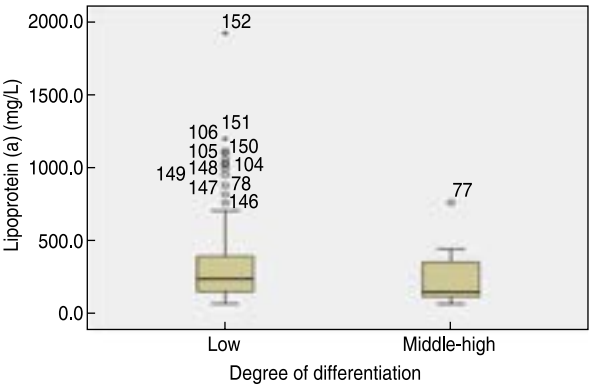

Fig. 3 Comparison according to the degree of differentiation. Note: Patients with highly differentiated and moderately differentiated gastric cancer were few and were thus combined into one group

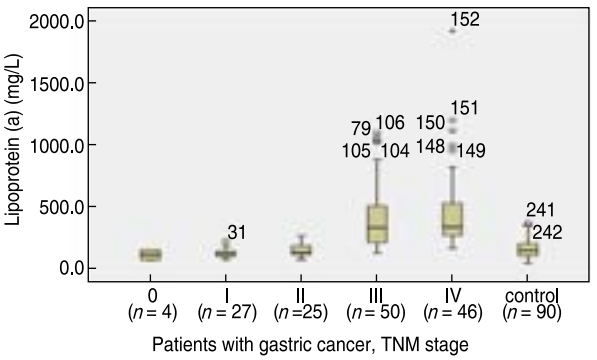

Fig. 2 Differences in lipoprotein (a) level among male patients with gastric cancer according to TNM stage

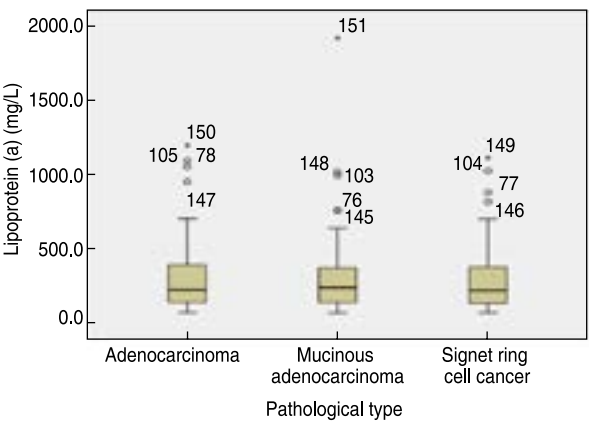

Fig. 4 Comparison of LP (a) concentration according to pathological type

Discussion

LP (a) is formed by binding to LDL through apo A disulfide bonds. It is synthesized and secreted from the liver into the blood. It is relatively stable in individual expression. It is not subject to dietary habits and geographical differences among the same race. The level of LP (a) varies greatly among different individuals and races, and the level of LP (a) is biased in the population. Estradiol-based estrogen promotes the synthesis of nucleic acids and proteins in target cells such as uterus, promotes cell growth, raises plasma α-globulin, increases plasma alpha-lipoprotein levels, and lowers LDL and cholesterol levels. Estrogen (mainly estradiol) promotes the synthesis of nucleic acids and proteins in uterine and other target cells, promotes cell growth, increases plasma

Table 1 Clinical characteristics of male gastric cancer patients and male health checkup personnel (*n*)

Variable		CIS	I	II	III	IV	Healthy people
Age (years)		64.00 ± 12.73	58.27 ± 8.48	55.22 ± 11.40	59.33 ± 10.88	58.7 ± 10.29	58.18 ± 11.42
BMI (kg/m^2)		21.59 ± 3.23	22.21 ± 1.23	22.19 ± 1.27	21.75 ± 1.49	21.45 ± 1.67	21.27 ± 1.43
Lipoprotein (a) (mg/L)		116.50 ± 23.39	127.82 ± 6.92	149.04 ± 10.53	405.30 ± 36.62	469.07 ± 49.60	169.08 ± 8.56
Degree of differentiation	Low	1	20	20	43	43	
	Middle-high	3	7	5	7	3	
Nerve invasion	+	1	2	13	42	33	
	–	3	25	12	8	13	
Vascular invasion	+	0	1	11	35	31	
	–	4	26	14	15	15	

alpha-globulin level, increases plasma alpha-lipoprotein levels, and reduces LDL and cholesterol levels. Studies have shown [14] that apo A, a component of LP (a), has 80% homology with plasminogen. LP (a) which has no fibrinolytic activity, can compete with plasminogen for the binding sites of fibrinogen monomer, inhibit the activation of plasminogen, and lead to local thrombosis and fibrinogen network. This is not only conducive to the adhesion of tumor cells to blood vessels, but also at the corresponding sites, platelet-derived growth factor can also be activated to promote the proliferation and growth of tumor cells. Other studies have shown that [15] LP (a) initiation involves a series of complex changes, such as complement activation, peptide release and chemotaxis, which play an important role in the development of tumors. In addition, some researchers [16] found apo A mRNA in cancer cell lines, so the process of cell proliferation may be due to gene mutations in the synthesis of apo A resulting in an increase in the blood level of LP (a). Some studies suggest that estrogen stimulates cells to secrete LDL receptor mRNAR. LP (a) is structurally similar to LDL. In addition to the component containing LDL (apo B 100), there is a special antigenic component apo A. LP (a) combines apo A with apo B 100 by disulfide bonds [17]. Decreased levels of estrogen can decrease plasma alpha-globulin, decrease plasma alpha-lipoprotein level, increase LDL level, and increase LP (a) level [18]. Decreased estrogen levels in postmenopausal women increase LP (a) levels, interfering with the level of LP (a) in gastric cancer patients compared with healthy people, hence the high incidence of gastric cancer among the middle-aged and elderly.

Firstly, the results of this study showed that male gastric cancer patients had significantly higher LP (a) levels and abnormal rates than normal people. Cao Chun [19] and other authors reported that serum LP (a) levels among cancer patients including lung cancer patients were significantly higher than those of normal people. It is suggested that high concentration of LP (a) may play a role in promoting tumor progression, which may be related to the fibrinolytic system and coagulation. The study also found that LP (a) levels and abnormal rates in male patients with stage I, stage II, stage III and IV gastric cancer were increasing. LP (a) levels in patients with carcinoma *in situ* were higher than those in patients with stage I and stage II disease, with small sample size bias not included in the comparison. This was consistent with the reports of Yang *et al* [14, 20–21] and other reports that the expression of lipoprotein in male lung cancer patients with stage I, II and III disease was increasing. The statistical results of this study showed that LP (a) levels were positively correlated with neurological invasion, vascular invasion, and positive and negative comparison. LP (a) may play a role in tumor angiogenesis. LP (a) contains apo A. In animal experiments [3], recombinant apo A inhibited the formation of capillary-like structures induced by basic fibroblast growth factor and tumor necrosis factor alpha. It is speculated that increased LP (a) concentration in solid tumor patients may be the regulatory mechanism of LP (a) expression under these conditions, and this may also be the case in gastric cancer. However, the specific mechanism is unclear and needs further studies to be elucidated.

The level of LP (a) in stage IV patients was higher than that in stage III patients, but the *P* value was higher than 0.05. The difference was not statistically significant. This result was contrary to that of Yang *et al* [14, 20–22] in their study of male lung cancer, but the level of LP (a) in stage IV patients was lower than that in stage III patients. In fact, the level of LP (a) in patients with stage IV disease is inconsistent. The reason may be that there are differences in the level of LP (a) between different races. LP (a) is relatively stable in individual expression, and is not subject to dietary habits and geographical differences between races, but largely depends on genes, so there may be great differences between races. The results showed that LP (a) level in poorly differentiated gastric cancer patients was higher than that in moderately-well differentiated gastric cancer patients, suggesting that the level of LP (a) might be an indicator of prognosis in gastric cancer patients, but there was no significant difference in LP (a) level between different pathological types. At present, there are no other similar or similar experimental studies, and much data need to be confirmed.

Conclusion

The aim of this study was to investigate the expression and clinical significance of serum LP (a) in patients with gastric cancer. Serum LP (a) level in patients with gastric cancer was significantly higher than that in the normal control group. The later the stage, the higher was the LP (a) level; there was also a negative correlation between LP (a) and the degree of differentiation of gastric cancer. The lower the degree of differentiation, the higher was the level of LP (a), and the correlation between LP (a) and the occurrence and development of gastric cancer. Because the experimental population selected in this experiment was mainly diagnosed and treated in recent years, it was impossible to calculate the survival period. It is not yet possible to study the relationship between LP (a) and prognosis. However, many studies have reported on the relationship between serum LP (a) levels and malignancies such as lung cancer and hematologic malignancies. The prognosis of tumors showed positive correlation. As the LP (a) level increased, the prognosis was worse. The relationship between the serum LP (a) and the prognosis of gastric cancer patients was considered as a follow-up research topic. In the future, serum LP (a) concentration

may be used as an indicator to analyze the staging and prognosis of gastric cancer, but the specific mechanism requires further research and a large amount of clinical data is needed.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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