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The Relationship between Gastric Secretion and Type of Early Gastric Carcinoma

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ABSTRACT

To determine the relationship between gastric secretion and gastric carcinoma, we investigated gastric acid secretion and the fasting serum levels of pepsinogen I and gastrin in 50 Japanese patients with early gastric carcinoma. After the histological and macroscopic type of carcinoma had been determined, results were compared with findings in 50 Japanese control subjects whose gastric mucosa was endoscopically normal. The maximum gastric acid secretion and fasting levels of serum pepsinogen I were significantly lower in intestinal type gastric carcinoma than in diffuse type carcinoma and in the controls. They were also significantly lower in the non-ulcerative (elevated or flat) type than in the ulcerative (depressed) type of carcinoma. The serum gastrin levels in patients with early gastric carcinoma of either the intestinal or diffuse type were higher than those in the control subjects, though the difference was not significant. Gastric acid secretion and serum pepsinogen I levels were related with both the histological and macroscopic types of gastric carcinoma. These findings suggest that the serum pepsinogen I level might be useful as a maker for early gastric carcinoma of the intestinal type.

Key words: *Gastric carcinoma, Gastric acid secretion, Serum pepsinogen I, Serum gastrin*

A close relationship has been shown to exist between the presence of achlorhydria and the development of gastric carcinoma[2,6,18]. Considering the relationship between gastric acid secretion and gastric carcinogenesis, the nitrosamine hypothesis has been reported as a significant factor[1,4,10,11] i.e., that the high intragastric pH in hypochlorhydria promotes the growth of nitrate-reducing bacteria that convert dietary amines, in the presence of the formed nitrite, into N-nitroso compounds which are potential carcinogens. Thus, it is important to clarify the relationship between the secretion of gastric acid and gastric carcinoma. We previously reported that, in Japanese subjects, the development of polypoid-type early gastric carcinoma was associated with type B atrophic gastritis[3].

Our objective in this study was to investigate the relationship between gastric acid secretion and the histological type of early gastric carcinoma as compared with secretion in endoscopically normal control subjects. In addition, we wanted to clarify the relationship between the macroscopic type of gastric carcinoma and gastric acid secretion. The serum levels of pepsinogen I and gastrin in gastric carcinoma were also evaluated.

PATIENTS AND METHODS

We evaluated subjects who had received endoscopic examinations at the First Department of Internal Medicine of Hiroshima University Hospital. There were 50 patients with early gastric carcinoma, 35 males and 15 females, whose mean age was 63.3±12.5 years (range 28–80 years), and 50 control subjects without gastric lesions at endoscopic examination, 20 males and 30 females, whose mean age was 56.2±9.0 years (range 40–83 years). The controls underwent endoscopic examinations because of their symptoms and included cases with atrophic gastritis. This study was performed under informed consent, and was retrospective study. We selected for study patients with early stage gastric carcinomas (limited to submucosal layers) because the stomachs of those with a more advanced disease were deeply or largely involved and thus may have lost their original secretory function. The carcinomas were divided by their histological type into two groups, the intestinal or diffuse type, according to Lauren's criteria[9]. They were also

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classified macroscopically into two groups according to the guideline for early gastric carcinoma presented by the Japanese Gastroenterological Endoscopy Society[8]. One group was the "elevated or flat" type consisting of protruded (I), superficial-elevated (IIa) and flat (IIb) types, defined in this study as the non-ulcerative type. The other group consisted of the "depressed" type which contained superficial-depressed (IIc) and excavated (III) types, defined in this study as the ulcerative type.

Considering the relationship between the histological type and macroscopic type of gastric carcinoma, most of the gastric carcinomas of the intestinal type (31 out of 39 cases) were of the non-ulcerative type. However, all but one of the gastric carcinomas of the diffuse type (11 out of 12 cases) were of the ulcerative type.

The methods for measuring gastric acid secretion, serum pepsinogen I and gastrin levels were previously described[3,17,19]. In brief, gastric acid secretion was measured at baseline to determine the basal acid output (BAO) (mEq/hr) and, following stimulation with tetragastrin (4μg/kg), to determine maximum acid output (MAO) (mEq/hr)[19]. The fasting serum levels of pepsinogen I and of gastrin were determined by radioimmunosorbent techniques[17].

Statistical method: Values were presented as mean ± standard error of means (SEM). Analysis of covariance was used to determine the statistical significance of the differences between groups. The significance level was set at 5 % for each analysis.

RESULTS

Acid output (BAO and MAO) and serum levels of pepsinogen I and of gastrin are shown in Table 1. Both BAO and MAO in the patients with gastric carcinoma was significantly lower than in the controls. Acid output decreased in this order: control, diffuse type, and intestinal type of carcinoma. MAO was significantly lower in the intestinal type of gastric carcinoma than in either the diffuse type or the controls. Gastric acid secretion was significantly lower in the non-ulcerative (elevated or flat) type than in the ulcerative type or the controls. The MAO decreased in this order: control, ulcerative type, and non-ulcerative type of carcinoma. Gastric acid secretion was related with both the histological and macroscopic types of gastric carcinoma.

Serum pepsinogen I was significantly lower in gastric carcinoma of the intestinal type than in either the diffuse type or the controls. Pepsinogen I was significantly lower in the non-ulcerative type of gastric carcinoma than in either the ulcerative type of gastric carcinoma or the controls. The serum levels of pepsinogen I in diffuse or ulcerative type gastric carcinoma did not differ significantly from control values.

Serum gastrin levels in patients with early gastric carcinoma of either the intestinal or diffuse type were higher than in the control subjects; however, the difference was not significant.

DISCUSSION

This study showed an association between gastric secretion and the type of early gastric carcinoma in Japanese subjects. A close relationship between hypo- or achlorhydria and gastric carcinoma of either the intestinal or non-ulcerative type was revealed. Atrophic gastritis is generally thought to be an associated lesion of gastric carcinoma[13,14,16,22]. Our results support this view, with the provision that atrophic gastritis was diagnosed not by histological examination, but by the determination of gastric acid secretion. However, the gastric acid secretion corresponded well with the number of parietal cells in the fundus. Hypochlorhydria and achlorhydria are caused by the progression of severe atrophic gastritis that diffusely involves the fundus. The diagnosis of atrophic gastritis is usually based on the results of histological examination of a specimen obtained by endoscopic biopsy or in a resected specimen. However, the presence of atrophic gastritis is often "patchy", and histological examination

Table 1. Gastric acid secretion, serum pepsinogen I and serum gastrin

	No of cases	BAO# (mEq/hr)	MAO## (mEQ/hr)	Serum Pepsinogen I (ng/ml)	Serum Gastrin (pg/ml)
Control	50	1.440 ± 0.257	8.852 ± 0.911	63.5 ± 4.5	116.6 ± 11.7
Gastric carcinoma					
Intestinal type	38	0.116 ± 0.023[a]	0.889 ± 0.177[a,b]	40.5 ± 5.4[a,b]	179.0 ± 28.5
Diffuse type	12	0.690 ± 0.303[a]	5.434 ± 1.658[a]	83.0 ± 18.7	192.9 ± 38.9
Non-ulcerative type	31	0.101 ± 0.026[a,c]	0.679 ± 0.137[a,c]	37.9 ± 6.3[a,c]	185.0 ± 32.3
Ulcerative type	19	0.488 ± 0.199[a]	4.103 ± 1.134[a]	71.4 ± 12.5	178.3 ± 33.8

#BAO: basal acid output, ##MAO: maximum acid output

$p<0.05$, a: *vs.* control, b: *vs.* diffuse type, c: *vs.* ulcerative type

may not reflect the status of the entire gastric mucosa. Hypochlorhydria and achlorhydria may indicate more accurately the presence of severe atrophic gastritis than histological examination.

The intestinal and diffuse types of gastric carcinoma have a different pathogenesis with regard to atrophic gastritis[13,14,20,23]. Atrophic gastritis is more common in the intestinal type, while in the diffuse type of gastric carcinoma atrophic gastritis is less recognized. Tatsuta et al[20] demonstrated a close relationship between the gross and histological types of early gastric carcinomas and the acid-secreting area as investigated by the Congo red test used at endoscopy. These investigators reported that when the acid secreting area was large, the carcinomas were ulcerated and histologically undifferentiated, whereas, when the acid secreting area was small, the carcinomas were polypoid and histologically differentiated. Our present results support these reports.

While the serum pepsinogen I level has been related to acid output in most subjects[12], the serum pepsinogen I level in our investigation was significantly lower in the intestinal and non-ulcerative types of gastric carcinoma compared with the diffuse and ulcerative types, or with the controls. Therefore, the use of serum pepsinogen I alone may offer advantages in screening for patients with atrophic gastritis, who are at high risk for the intestinal type of gastric carcinoma. Varis et al[21] pointed to the usefulness of screening for atrophic gastritis by measuring the levels of both serum pepsinogen and gastrin.

The pathogenesis of the diffuse type of gastric carcinoma is not clearly related to the presence of atrophic gastritis, hypochlorhydria or hypergastrinemia[13,14,23]. Our study did not clarify the risk factors for this type of gastric carcinoma.

Serum gastrin levels in patients with early gastric carcinoma of either the intestinal or diffuse type were higher than in the control subjects, while the difference was not significant. It is suggested that increased levels of serum gastrin in carcinomas might be due to a feed-back against decreased gastric acid secretion.

A previous study[3] showed that mild hypergastrinemia was due to gastritis. However, it has also been suggested that hypergastrinemia may influence the development of gastric carcinoma or carcinoid tumor[5,23]. Correa et al[1] proposed a multi-stage process in which the key events represent changes in the microenvironment composed of the gastric mucosa and the stomach content. The first step involves the development of chronic superficial gastritis, which can be induced by ingesting irritants such as salt in excessive quantity, aspirin and alcohol, which then leads to atrophic gastritis. This produces hypochlorhydria and allows the growth of bacteria in the gastric lumen[4,11]. Bacterial overgrowth is capable of reducing dietary nitrate to nitrite and further reducing nitrite to N-nitroso compounds, which are supposed to be carcinogenic materials for gastric carcinoma while in hypothesis[7,15].

In conclusion, we found that the gastric acid secretion and level of fasting serum pepsinogen I were both significantly decreased in gastric carcinoma, while the fasting level of serum gastrin was not significantly increased. This trend was more apparent with the intestinal or non-ulcerative types of gastric carcinoma. These findings suggested that the serum pepsinogen I level might be useful as a maker for early gastric carcinoma of the intestinal type.

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REFERENCES

1. **Correa, P.** 1988. A human model of gastric carcinogenesis. Cancer Res. **48:** 3554–3560.
2. **Grossman, M.I., Kirsner, J.B. and Gillespie, I.E.** 1963. Basal and histalog-stimulated gastric secretion in control subjects and in patients with peptic ulcer or gastric cancer. Gastroenterology **45:** 14–26.
3. **Haruma, K., Yoshihara, M., Sumii, K., Tari, A., Watanabe, C., Kodoi, A. and Kajiyama, G.** 1993. Gastric acid secretion, serum pepsinogen I, and serum gastrin in Japanese with gastric hyperplastic polyps or polypoid-type early gastric carcinoma. Scand. J. Gastroenterol. **28:** 633–637.
4. **Hill, M.J., Hawksworth, G. and Tattersall, G.** 1973. Bacteria, nitrosamines and cancer of the stomach. Br. J. Cancer **28:** 562–567.
5. **Hirschowitz, B.I., Griffith, J., Pellegrin, D. and Cummings, O.W.** 1992. Rapid regression of enterochromaffinlike cell gastric carcinoids in pernicious anemia after antrectomy. Gastroenterology **102 (4Pt1):** 1409–1418.
6. **Hitchcock, C. R., Sullivan, W. A. and Wangensteen, O. H.** 1955. The value of achlorhydria as a screening test for gastric cancer. A 10-year report. Gastroenterology **29:** 621–628.
7. **Houghton, P.W.J., Leach, S., Owen, R.W., McC Mortensen, N.J., Hill, M.J. and Williamson, R.C.N.** 1980. Use of a modified N-nitrosoproline test to show intragastric nitrosation in patients at risk of gastric cancer. Br. J. Cancer **60:** 231–234.
8. **Japanese Research Society for Gastric Cancer.** 1973. The general rules for gastric cancer. Jpn. J. Surg. **3:** 61–71.
9. **Lauren, P.** 1965. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. Acta Path. Microbiol. Scand. **64:** 31–49.
10. **Reed, P.I., Smith, P.L.R., Haines, K., House, F.R. and Walters, C.L.** 1981. Gastric juice N-nitrosamines in health and gastroduodenal disease. Lancet **2:** 550–552.
11. **Ruddell, W.S.J., Bone, E.S., Hill, M.J., Blendis, L.M. and Walters, C.L.** 1976. Gastric juice nitrite: a risk factor for cancer in the stomach? Lancet **2:** 1037–1069.

12. **Samloff, I.M., Secrist, D.M. and Passaro, E.Jr.** 1975. A study of the relationship between serum group I pepsinogen levels and gastric acid secretion. Gastroenterology **69:** 1196–1200.
13. **Sipponen, P., Kekki, M. and Siurala, M.** 1983. Atrophic chronic gastritis and intestinal metaplasia in gastric carcinoma. Cancer **52:** 1062–1068.
14. **Sipponen, P., Kekki, M. and Siurala, M.** 1984. Age-related trends of gastritis and intestinal metaplasia in gastric carcinoma patients and in controls representing the population at large. Br. J. Cancer **49:** 521–530.
15. **Stemmermann, G.N. and Mower, H.** 1981. Gastritis, nitrosamines, and gastric cancer. J. Clin. Gastroenterol. **3:** 23–27.
16. **Strickland, R.G. and Mackay, I.R.** 1973. A reappraisal of the nature and significance of chronic atrophic gastritis. Am. J. Dig. Dis. **18:** 426–440.
17. **Sumii, K., Inbe, A., Uemura, N., Kimura, M., Haruma, K., Yoshihara, M., Teshima, H., Kajiyama, G. and Miyoshi, A.** 1989. Increased serum pepsinogen I and recurrence of duodenal ulcer. Scand. J. Gastroenterol. **24:** 1200–1204.
18. **Svendsen, J.H., Dahl, C., Svendsen, L.B. and Christiansen, P.M.** 1986. Gastric cancer risk in achlorhydric patients. A long-term follow-up study. Scand. J. Gastroenterol. **21:** 16–21.
19. **Tahir, H., Sumii, K., Haruma, K., Tari, A., Uemura, N., Shimizu, H., Sumioka, M., Inaba, Y., Kumamoto, T., Matsumoto, Y., Sanuki, E., Hirata, K., Suenaga, K., Hidaka, T., Kajiyama, G. and Miyoshi, A.** 1984. A statistical evaluation on the age and sex distribution of basal serum gastrin and gastric acid secretion in subjects with or without peptic ulcer disease. Hiroshima J. Med. Sci. **33:** 125–130.
20. **Tatsuta, M., Okuda, S., Taniguchi, H. and Tamura, H.** 1979. Gross and histological types of early gastric carcinomas in relation to the acid-secreting area. Cancer **43:** 317–321.
21. **Varis, K., Kekki, M., Härkönen, M., Sipponen, P. and Samloff, I.M.** 1991. Serum pepsinogen I and serum gastrin in the screening of atrophic pangastritis with high risk of gastric cancer. Scand. J. Gastroenterol. Suppl. **186:** 117–123.
22. **Walker, I.R., Strickland, R.G., Ungar, B. and Mackay, I.R.** 1971. Simple atrophic gastritis and gastric carcinoma. Gut **12:** 906–911.
23. **Waldum, H.L., Petersen, H. and Brenna, E.** 1992. Gastrin and gastric cancer. Eur. J. Gastroenterol. Hepatol. **4:** 801–811.