Acta Med. Nagasaki 39:16－20

A Clinical Study on Serum Pepsinogen in 81 Patients Undergoing Gastric Examination

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The serum pepsinogen (PG) level was determined in 81 patients undergoing gastric examination, and the results were clinically compared with the results of the conventional primary screening for gastric cancer based on the inquiry and radiography of the upper digestive tract. The values of PG I and PG II in patients whose stomach was found to be normal (normal group) were almost the same as the reported values, but their PG I /PG II ratio was somewhat smaller than the reported value.

The PG levels in the gastric ulcer, erosive gastritis and gastric polyp groups did not significantly differ from those in the normal group, while the screening based on the PG level was suggested to be potentially useful for discovery of atrophic gastritis, post-gastrectomy abnormality and duodenal ulcer.

Gastric cancer was discovered in four of the 81 cases (early cancer in one case and advanced cancer in three cases), and all were poorly-differentiated adenocarcinoma. When compared with the normal group, only the PG I / II ratio was smaller in this group. If this PG method is employed for the primary screening, the false-positive rate is 35.5% (false-negative rate:75%), an 46.9% of subjects undergoing this screening will require a second examination. The discrepancy between the results of this study and those reported earlier was surmised to be partly attributable to the facts that histological type was poorly-differentiated adenocarcinoma in all the patients with gastric cancer in this study and the mean age of all subjects was more than 10 year higher than that in the earlier report. Compared with the conventional screening method, the percentage of subjects requiring a second examination was higher by more than 20%. It was concluded that further studies are necessary, including review of the criteria for judgment of gastric cancer.

Introduction

Pepsinogen (PG) is an inactive precursor of pepsin, an offensive factor involved in the developmental mechanism of peptic ulcers, and immunochemically-different two groups, pepsinogen I (PG I) and pepsinogen II (PG II), have been identified.[1]

Their localization and distribution in the stomach differ from those in the duodenum; PG I exists in the fundic gland region, while PG II exists in not only the fundic gland region but also cardiac, pyloric and duodenal gland regions. It has been reported that, in healthy persons, only PG I is excreted into the urine.[2]

The presence of PG in the blood was first recorded by Van Calcar in 1912. About 50 years later, Miki et al. and Samloff et al. developed radioimmunoassay (RIA)[3,4], of PG I and PG II in 1981 and enzyme linked immunosorbent assay (ELISA)[5] of these in 1987; by these methods, it has become possible to determine the concentration of PG in the blood. Since then, the pathophysiological and clinical significance of PG has been rapidly elucidated.[3,4] The serum PG level is ralated to pathology, such peptic ulcers (particularly, recurrent intractable peptic ulcer), Zollinger-Ellison syndrome, pernicious anemia, renal failure, gastrectomized stomach, atrophic gastritis and acute gastric (mucosal) lesion. It is also expected that the serum PG level can be used as an indicator of screening for gastric cancer, and it has been being studied to this end.[3,6,7]

In 1988, DAINABOT Co. developed an RIA kit, and it has widely been used because of its convenient and highly-reproducible nature.[6] With the objective of investigating whether serum PG level is useful as an indicator of gastric cancer in its primary screening, we determined, using said RIA kit, the levels of PG I and PG II in patients who visited our hospital to undergo examination for gastric cancer. This study is reported below.

I. Subjects and Methods

The subjects of this study were 81 patients who visited our hospital to undergo examination for gastric cancer during the one-month period from October into November, 1991. Their age ranged from 32 to 89 years (mean:55.6 ± 12.0 years), and they consisted of 43 males and 38 females. In all 81 cases, PG I and PG II were determined, and either

upper digestive tract radiography or gastroduodenal endoscopy, or both, were performed. Determination of the serum PG I and PG II levels was requested to BML (Biochemical Medical Laboratory) and performed by the RIA method.

Parameters analyzed in this study were the PG I level, PG II level, PG I /PG II ratio, age and their correlation with diseases of the upper digestive tract (chronic gastritis, paptic ulcer, gastric polyp, postgastrectomy abnormality and gastric cancer).

Normal ranges of PG I , PG II and PG I /PG II values were defined as mean $\pm$2 S.D. of respective values in the normal group (patients found to be free of gastric diseases). The statistical analysis was performed by Student's t-test and Welch's method, and $P<0.05$ was defined as statistically significant.

II. Results

1. Results of Examination of Upper Digestive Tract (by radiography or endoscopy or both)

There were no particular abnormalities detected in 31 cases (defined as the normal group), while some kind of abnormality was discovered in the remaining 50 cases. The abnormalities consisted of gastric ulcer in 7 cases, duodenal ulcer in 4 cases, gastroduodenal ulcer in one case, gastric cancer in 4 cases, gastric polyps in 5 cases, erosive gastritis in 7 cases, atrophic gastritis in 19 cases and abnormality relating to earlier partial gastrectomy in 3 cases (Table 1).

2. Serum PG I Level (Fig.1)

The mean value of the serum PG I in the 81 cases was 52.2$\pm$31.1 ng/ml. The mean value in the male subjects was 44.8$\pm$24.4 ng/ml, while it was 60.6$\pm$35.5 ng/ml in the female subjects; the PG I level was significantly($P<0.05$) higher in the female group. In the normal group (n=31), the mean value was 53.7$\pm$25.8 ng/ml. The mean values in each disease group were as follows: gastric ulcer (n=7), 4 4.5$\pm$21.7 ng/ml; duodenal ulcer (n=4), including gastroduodenal ulcer), 103.6$\pm$61.7 ng/ml; gastric cancer (n=4), 72.5$\pm$28.8 ng/ml; gastric polyp (n=5), 55.4$\pm$7.6 ng/ml; erosive gastritis (n=7), 40.0$\pm$13.7 ng/ml; atrophic gastritis (n=19), 41.8$\pm$20.5 ng/ml; and gastrectomy (n=3), 15.9$\pm$7.4 ng/ml. When compared with the normal group, the PG I level was significantly ($P<0.01$) higher in the duodenal ulcer group, while it was significantly ($P<0.01$) lower in the gastrectomy group. No significant difference was noted with the groups of gastric cancer, gastric polyp, gastric ulcer or chronic gastritis.

3. Serum PG II Level (Fig.2)

The mean PG II value was 19.3$\pm$11.8 ng/ml in all cases, 16.3$\pm$10.1 ng/ml in the male group, and 22.7$\pm$12.6 ng/ml

Table 1 The subjects who visited Matsuura municipal hospital for the purpose to undergo examination for gastric cancer during a month.

	Male	Female	Total
Normal	19	12	31
Gastric ulcer	4	3	7
Duodenal ulcer	2	2	4
Gastroduodenal ulcer	0	1	1
Gastric cancer	2	2	4
Gastric polyp	1	4	5
Gastrectomy	2	1	3
Atrophic gastritis	10	9	19
Erosive gastritis	3	4	7
Total	43	38	81

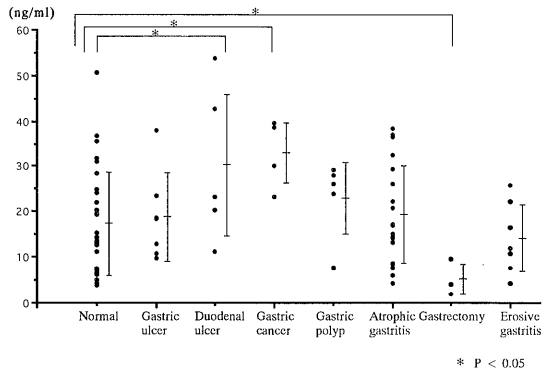

Fig.1 Correlations between serum PG I levels in normal group, gastric ulcer group, gastric polyp group, atrophic gastritis group, gastrectomy group, and erosive gastritis group.
Compared with normal subjects, serum PG I levels was significantly higher in duodenal ulcer patients (included one gastroduodenal ulcer patient), lower in gastrctomy patients. No significant different was not shown other groups.

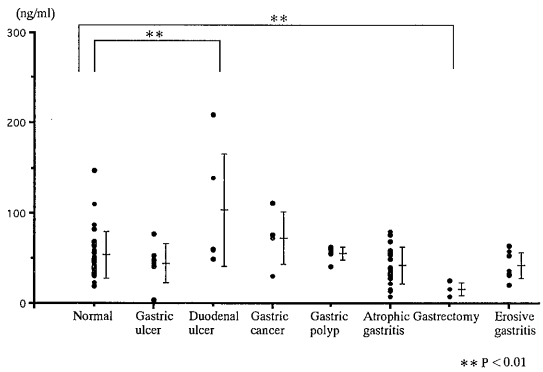

Fig.2 Correlations between serum PG II levels in normal group, gastric ulcer group, gastric polyp group, atrophic gastritis group, gastrectomy group, and erosive gastritis group.
Compared with normal subjects, PG II levels was significantly higher in duodenal ulcer patients and gastric cancer patients, while it was significantly lower in gastrectomy patients.

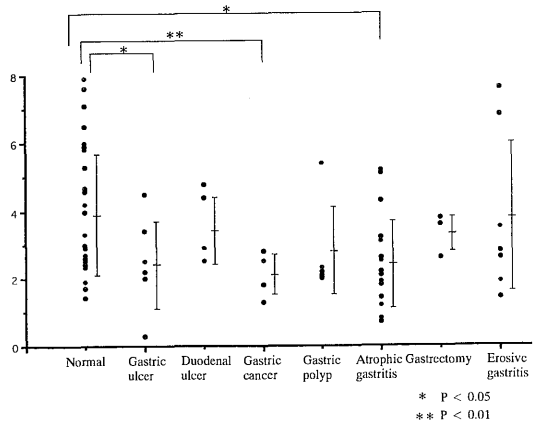

Fig.3 Correlations between serum PG I / II ratio levels in normal group, gastric ulcer group, gastric polyp group, atrophic gastritis group, gastrectomy group, and erosive gastritis group.
Compared with normal subjects, PG I /PG II ratio level was significantly lower in gastric ulcer patients, gastric cancer patients and atrophic gastritis patients.

in the female group. The difference between the male and female group was not significant.

In the normal group, the mean value was 17.4±11.4 ng/ml. The mean values in each disease group were as follows: gastric ulcer, 18.8±9.7 ng/ml; duodenal ulcer, 30.3±15.6 ng/ml; gastric cancer, 32.9±6.7 ng/ml; gastric polyp, 22.9±7.9 ng/ml; erosive gastritis, 14.2±7.2 ng/ml; atrophic gastritis, 19.4±10.8 ng/ml; and gastrectomy, 5.2±3.2 ng/ml. When compared with the normal group, the mean level was significantly higher in the duodenal ulcer group ($P<0.05$), and gastric cancer group ($P<0.05$), while it was significantly lower in the gastrectomy group ($P<0.05$).

4. PG I /PG II Ratio (Fig.3)

The mean value of the PG I /PG II ratio in the 81 cases was 3.2±1.7. The mean value in the male subjects was 3.2±1.7, while it was 3.2±1.6 in the female subjects; the difference was not significant. In the normal group, the mean value was 3.9±1.8. The mean values in each disease group were as follows: gastric ulcer, 2.4±1.3; duodenal ulcer, 3.4±1.0; gastric cancer, 2.1±0.6; gastric polyp, 2.8±1.3; erosive gastritis, 3.8±2.2; atrophic gastritis, 2.4±1.3; and gastrectomy, 3.3±0.5. When compared with the normal group, the mean level was significantly lower in the gastric ulcer group ($P<0.05$), gastric cancer group ($P<0.05$) and atrophic gastritis group ($P<0.01$).

Discussion

In Japan, the malignant tumor with the highest incidence and the highest mortality is still gastric cancer. With this background, efforts have been made to develop a screening method which is simple, convenient and highly specific for gastric cancer. Since 1962, fluorography of upper digestive tract has been employed as the method of primary mass screening for gastric cancer, and this approach has been effective to a considerable degree. However, problems relating to examination time and exposure dose of x-ray remain unsolved. The problem concerning the dose of x-ray can be avoided by introducing endoscopic approach, but it is more painful for patients than fluorography. In 1982, Ichinose et al.[3] reported that the serum pepsinogen (PG) level is a useful criterion for screening for gastric cancer. This finding has urged us to compare its effectiveness with that of the conventional screening method for gastric cancer.

We measured the serum PG level in all outpatients who visited our hospital during a one-month period using the PG I /PG II RIA kit of DAINABOT Co. and studied its relationship with diseases of the upper digestive tract. The normal value of PG is not affected by sex, human race, season, etc., but affected by aging.[3,6,7] In our present study, the values of PG I and PG II in normal subjects did not differ from the reported values, but the PG I /PG II ratio in these subjects tended to be smaller than the reported ratio. This result is surmised to be due to the fact that the mean age of these subjects was larger by more than 10 years than that of the subject group in the earlier report.

In general, the value of PG I does not change during human life from the second decade through the seventh decade, while the value of PG II gradually increases from the second decade through the sixth decade, and the PG I / PG II ratio gradually decreases from the second decade through the sixth decade.[6] Similar tendencies were observed in our present study as well. That is, the value of PG I was not dependent on age ($y=0.66x+20.8$; $r^2=0.21$; NS), while the value of PG II tended to increase gradually with aging ($y=0.45x-5.1$; $r^2=0.21$; $P<0.01$). The PG I /PG II ratio tended to decrease gradually in association with aging ($y=-0.06x+6.8$; $r^2=0.142$; $P<0.05$).

It is believed that the state of chronic gastritis and atrophy of the fundic gland can be estimated based on the value of PG and PG I /PG II ratio. Namely, Samaioff et al.[4,8] reported that the size of atrophic area in atrophic gastritis is significantly correlated with the value of PG I and PG I /PG II ratio. This is thought to be due to a reflection of the impaired exocrine function due to a decrease in the number or loss of the chief cells and parietal cells occurring in association with the progression of atrophy of the gastric mucosa.[9] In our present study, the PG I level did not differ significantly between the atrophic gastritis group and the normal group, but the PG I /PG II ratio was, as it was expected, significantly ($P<0.01$) smaller in the atrophic gastritis group. This is thought to indicate a relative decrease in the ability to secrete PG I.

It is generally believed that, in patients with gastric

ulcer, the value of PG II has been increased, and the PG I / PG II ratio has been decreased.[6,7] In the seven cases of gastric ulcer in our present study, the serum PG I and P G II values did not differ from those in the normal group, while the PG I /PG II ratio was significantly smaller in the gastric ulcer group ($P<0.05$). An imbalance between offensive and defensive factors is involved in the etiology of peptic ulcers, and hence analysis of only pepsin, an offensive factor, and PG, the precursor of pepsin, may be insufficient.

In patients with duodenal ulcer, the serum gastrin value has been usually increased, and secretion of gastric juice has also been increased in many cases. Gastrin is known to stimulate production of pepsin.[10] Probably for this reason, the increase in the PG I level is larger in duodenal ulcer than in gastric ulcer.[6,7] In fact, both the PG I and PG II levels were significantly higher in the duodenal ulcer group ($P<0.05$ for both). The PG I value in patients with recurrent ulcers has been reported to be high.[6] The subjects of the present study also included an interesting duodenal ulcer case with a PG I value of 208.5 ng/ml, a PG II value of 42.8 ng/ml and a PG I /PG II ratio of 4.8; the PG I value had been markedly increased, and duodenal ulcer had recurred three times during the previous two-year period. This case supports the report of Miki et al.[11] that the level of PG I predicts to some extent the risk of recurrence of ulcer in patients with peptic ulcers, especially duodenal ulcer.

The numbers of the patients with gastric polyps, gastric cancer and stomach undergoing gastrectomy were all small, and thus it was difficult to make detailed comparisons with the normal group. It is generally belived that the PG I value is comparatively small in patients with gastric polyps. This is considered to be due to atrophy, which is present along with gastric polyps.[3]

Gastric cancer was discovered in four of the 81 cases; three were advanced cancer, one was early cancer, and histological type was poorly differentiated adenocarcinoma in all four cases. It is of little value to say any relationship between gastric cancer and the PG level based on the data from these four cases. In this connection, it has been reported that the PG I value is generally small and PG I /PG II ratio is generally decreased in gastric cancer cases.[6,7,12] This is surmised to be due to the fact that well-differentiated adenocarcinoma develops in atrophic mucosa. Because the gastric cancer type poorly-differentiated adenocarcinoma in all four cases, it is thought that there was no difference in the PG I level and only PG I /PG II ratio was small.

The gastrectomy of the three cases was partial resection in all cases, and both the PG I and PG II values were significantly low compared with respective value in the normal group. As a matter of course, a decrease in the number of secretory cells is thought to be reflected on the level of PG of patients with resected stomach.

The Study Group on the pepsinogen RIA kits established the following criteria for judgment of gastric cancer in screening for gastric cancer based on the data obtained in various districts of Japan[6]: PG I <70 and PG I /PG II $<$ 3.0. When these criteria were applied to the results of the present study, 38 (46.9%) of the 81 cases can be judged to be positive for gastric cancer. Of the 31 cases in the normal group, 11 cases test positive based on these criteria. Consequently, the false-positive rate is 35.5%. Of the four cases in the gastric cancer group, only one case tests positive by the criteria. As described earlier, all these four cases had poorly-differentiated adenocarcinoma, and it is thus thought that screening based on PG level is inappropriate for these cases. On the other hand, in the 19 cases of atrophic gastritis, which is believed to be likely to develop well-differentiated adenocarcinoma,11 cases (58.9%) test positive based on the criteria; PG level is therefore thought to be more effective for screening of well-differentiated adenocarcinoma.

As described above, it is thought that the serum PG level as determined using the PG I /PG II RIA kit reflects well, as has been pointed out, the pathological and physiological state of secretion of acid and pepsin in gastric/duodenal diseases. In the present study, this approach using PG level was not very effective as a supportive means for diagnosis of gastric ulcer, erosive gastritis or gastric polyp, but it is thought to be useful for screening for atrophic gastritis, post-gastrectomy diseases and duodenal ulcer. However, our study demonstrated that 1) only 25.0% of the gastric cancer cases tested positive for this PG method, although the histological type was poorly-differentiated adenocarcinoma in all cases, and 2) when judged solely based on this method, as high as 46.9% of all the subjects, or nearly half, would require a second examination for gastric cancer. These results indicate that the screening using PG cannot replace, at least in this point of time, the conventional inquiry method plus fluorography of the upper digestive tract. It is necessary to conduct further studies on this approach, including revision of the criteria for judgment.

Acknowledgments

The authors thank all staff of Matsuura Municipal Hospital, Dr. Masuho Haraguchi, Dr. Hajime Tnioka at Department of Internal Medicine, Sasebo Municipal Hospital, for their many advises. Special thanks to BML co. for measurement of serum pepsinogen.

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