Duodenal ulcer is a multifactorial disorder — the role of pepsinogen I

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Abstract **Serum pepsinogen I (PGI) levels were measured in 231 duodenal ulcer (DU) patients and 100 sex- and age-comparable healthy controls. Significantly higher mean serum PGI levels were found in DU patients than in controls (124,7 ± 3,4 ng/ml v. 92,9 ± 2,3 ng/ml; $P < 0,001$) (mean ± SE). These levels were higher in male DU patients than in female DU patients (128,5 ± 3,9 ng/ml v. 107,4 ± 6,4 ng/ml; $P < 0,05$). Smoking was associated with elevated serum PGI levels in DU patients (145,3 ± 5,1 ng/ml v. 109,0 ± 4,2 ng/ml; $P < 0,001$). Healed DUs were associated with lower mean serum PGI levels than active ulcers (110,9 ± 7,6 ng/ml v. 129,4 ± 3,8 ng/ml, $P < 0,05$). Whether patients were positive or negative for *Helicobacter pylori*, infection did not affect mean serum PGI levels. All the risk factors for DU may not affect serum PGI levels and DU may therefore be considered a multifactorial disease.**

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Hypersecretion of acid and pepsin, either in basal or stimulated states, is believed to be the pathogenesis of duodenal ulcer (DU).[1] Acid secretory studies are inconvenient and time-consuming. Serum pepsinogen I (PGI) is a product of the chief mucous neck cells of fundic glands; its level is usually correlated with maximal acid output capacity and may represent the parietal cell mass of stomach.[2] Hyperpepsinogenaemia I exists among DU patients although there is marked overlapping with controls.[3] Smoking, emotional stress, family history and blood type O have been mentioned as risk factors for DU.[4-6] *Helicobacter pylori* (HP) infection is also currently being considered as a possible factor in the pathogenesis of DU.[7] The aims of the present study were to evaluate the clinical significance of serum PGI levels in Chinese DU patients and decide which common risk factors in DU might affect serum PGI levels.

Patients and methods

Two hundred and thirty-one patients with dyspepsia and endoscopic documentation of DU were studied at our gastro-enterology clinic. Those who had a history of stomach operations, gastric outlet obstruction, alcoholism, abnormal renal function tests, gastrinoma and intakes of salicylates, steroids, non-steroidal anti-inflammatory drugs, anticholinergics and anti-ulcer medications (except antacids) were excluded from the study. During endoscopy, the number and state of the ulcers were recorded. Healed DU was defined as a scar with the absence of an ulcer crater; anything else considered an active ulcer. Furthermore, 100 sex- and age-comparable healthy controls were studied (Table I). None of them showed signs of dyspepsia or had positive findings on endoscopy. Subjects who had smoked more than 10 cigarettes a day for at least 1 year were classified smokers. Those who smoked less or who had given up smoking less than a year before were excluded from the study. After patients had fasted overnight, venous blood samples were collected before an endoscopy was performed. Serum PGI levels were measured by the SB-PEPSI radio-immunoassay kits (International CIS, France). The intra-assay and interassay variability coefficients for PGI were 7,0% and 8,0% respectively. Serum gastrin (G-17) levels were measured with GammaDab [^{125}I] gastrin radio-immunoassay kits (Baxter Healthcare Corporation, Cambridge, Mass, USA). The intra-assay and interassay variability coefficients for gastrin were 7,7% and 8,8% respectively. Two specimens of antral mucosa were collected and cultured to determine the presence of HP.[8] The specimens were homogenised and inoculated over Mueller-Hinton agar. They were incubated at 37°C under micro-aerobic conditions for a week. Colonisation was tested for with various specific enzymes, and observed under a microscope to determine whether it was compatible with the characteristic of HP. All data were expressed as means ± SE. The chi-square test, Student's unpaired *t*-test, analysis of variance test and Pearson's correlation were used to calculate statistics. A *P*-value less than 0,05 was significant.

TABLE I.
Comparison of characteristics of DU patients and healthy subjects

	Duodenal ulcer ($N = 321$)		Healthy controls ($N = 100$)		
	No.	%	No.	%	*P*-value*
Males	192	83,1	80	80	*NS*
Smokers	100	43,3	24	24	< 0,001
Blood group					
A	54	23,4	26	26	
B	51	22,1	22	22	*NS*
AB	18	7,8	8	8	
O	108	46,8	44	44	
Mean age (yrs)	51,5 ± 1,0		49,9 ± 1,0		*NS*

* Student's *t*-test or χ^2 test. NS = not significant.

Results

Mean serum PGI levels were significantly higher in DU patients than in healthy controls (124,7 ± 3,4 ng/ml v. 92,9 ± 2,3 ng/ml; $P < 0,001$). If the cut-off value of 'normal' male serum PGI was defined as 150 ng/ml (mean ± 2 SD), 28,6% of male DU patients had elevated serum PGI levels. Among female DU patients, 35,9% had raised levels (> 125 ng/ml). Significant differences in PGI levels were demonstrated between the following groups: male healthy controls v. female healthy controls, male DU patients v. male healthy con-

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trols, female DU patients v. female healthy controls, and male DU patients v. female DU patients (Fig. 1). There was no correlation between serum PGI level and age in DU patients ($r = 0,129$). For the DU patients, the mean serum PGI level of 100 smokers was significantly higher than that of 131 non-smokers. Among male DU patients, 96 smokers also had significantly higher PGI levels than 96 non-smokers (Fig. 2). Mean serum PGI levels of DU patients classified into blood groups A, B, AB and O were 131,6 ± 7,1 ng/ml, 118,2 ± 5,8 ng/ml, 150,3 ± 15,4 ng/ml and 120,2 ± 5,2 ng/ml respectively. The differences were not significant. Mean serum PGI levels in 173 active DU patients and 58 healed DU patients were significantly different (129,4 ± 3,8 ng/ml v. 110,9 ± 7,6 ng/ml; $P < 0,05$). Of these 173 active DU patients, 127 with a single ulcer crater and 46 with two or more ulcer craters showed no difference in mean serum PGI levels (125,8 ± 5,2 ng/ml v. 118,8 ± 7,1 ng/ml; *NS*). Serum PGI and gastrin levels were determined simultaneously among 103 patients with active DU and a positive correlation was found in both cases ($r = 0,55$; $P < 0,0001$) (Fig. 3). Of 104 patients with DU, 73 (70,2%) were positive for HP infection. Mean serum PGI levels did not differ significantly from those of 31 DU patients who were negative for HP infection (122,8 ± 6,9 ng/ml v. 119,0 ± 9,1 ng/ml; *NS*)

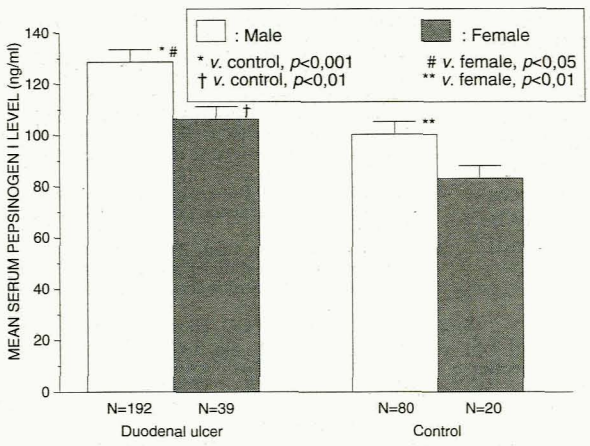

FIG. 1.
Comparisons of mean serum PGI levels of male DU patients, female DU patients, male healthy controls and female healthy controls. Vertical lines through bars indicate SEM. Significant differences exist between DU patients and controls.

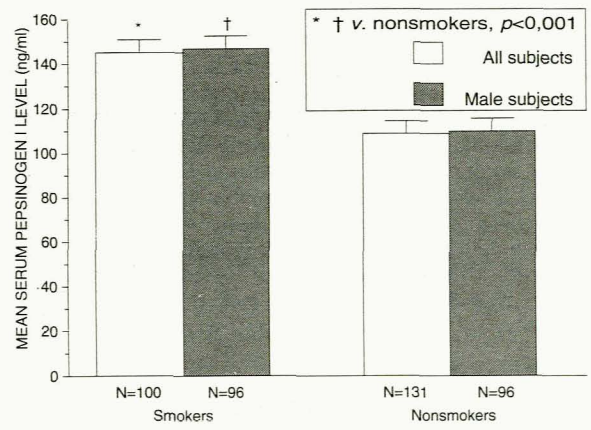

FIG. 2.
Comparison of mean serum PGI levels in smoking and non-smoking DU patients. Vertical lines through bars indicate SEM. Significant differences exist between smokers and non-smokers.

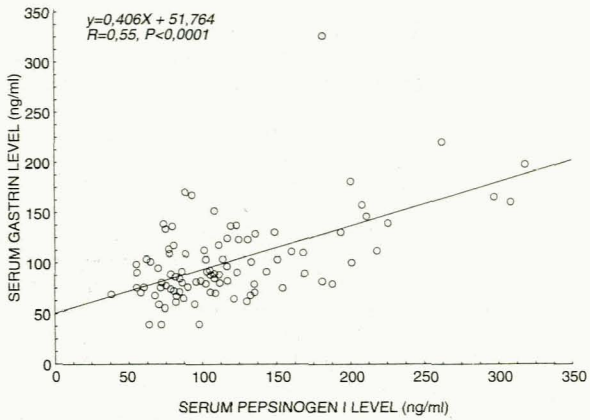

FIG. 3.
Positive correlation between serum PGI levels and gastrin levels in 103 patients with active DU; $r = 0,55$; $P < 0,0001$.

Discussion

The present study confirms higher serum PGI levels in Chinese DU patients than in controls, further supporting the contention that hypersecretion or hyperacidity is related to the pathogenesis of DU.[3,9,10] This pattern even occurs in children with DU.[11] Therefore, hyperpepsinogenaemia I in some DU patients can be inherited as an autosomal dominant trait.[11,12] One of the DU genes appears to determine serum PGI level, but we did not try to evaluate whether a family history of DU might influence the serum PGI levels of DU patients because many of the individuals studied were unaware of the definitions of DU, gastric ulcer and non-ulcer dyspepsia. Using serum PGI level as an auxiliary diagnostic modality, a low serum PGI level will exclude the diagnosis of DU.[13] However, considerable overlapping of serum PGI levels between DU patients and healthy controls probably precludes clinical diagnosis of DU for most patients without known historical, endoscopic or radiological data.

The severity of atrophic gastritis or gastric atrophy increases with age and should therefore result in the diminution of serum PGI levels in the elderly, as proved among controls.[3,10] In contrast, constantly higher PGI levels are reported in all aged DU patients, as we found in ours. The acid secretory capacity of DU patients appears to remain the same despite ageing.[10] Cigarette smoking has been emphasised as a major factor in the pathogenesis of DU.[14] There is a higher prevalence of smokers among DU patients (Table I) with significantly higher mean serum PGI levels, particularly male DU patients. Chronic smoking in DU patients appears to increase the acid secretory capacity; this is reflected in hyperpepsinogenaemia I.[4,15] Trophic effects on gastric acid and pepsin secretion caused by smoking through vagal tones in some DU patients, especially males, could therefore explain the heterogeneous disorders of DU.[15]

Blood group O has been associated with DU.[5] Nevertheless, the correlation between blood group and hyperpepsinogenaemia I has not been confirmed in DU patients or controls in recent studies, including ours.[4,16] It has been reported that pepsin secretion is indeed higher among patients with active DUs than among those with healed DUs.[17] The recurrence rate of DU when therapy is not maintained is significantly higher in hyper-PGI patients than in normo-PGI patients.[18] This seems to suggest that patients with active DUs will have higher serum PGI levels than those with healed DUs. We were able to prove a lower mean serum PGI level in patients with healed DUs than in those with active

DUs.[9,10] However, the number of ulcers did not determine the serum PGI level.

There is a relationship between gastrin, acid and PGI. Gastrin is normally secreted from the G-cells of antra and is responsible for stimulating acid secretion. Therefore, when hypergastrinaemia exists in the presence of hyperacidity, inappropriate and excessive acid secretion should be suspected.[19] Pentagastrin stimulation may also be responsible for higher serum PGI levels in DU patients.[20] Meanwhile, there is a familial type of antral G-cell hyperfunction which manifests as basal postprandial hypergastrinaemia, hyperpepsinogenaemia I, and DU.[21] We observed a positive correlation between serum PGI and gastrin levels in active DU patients, the reason for which is unknown. Nevertheless, it was impossible for all our patients to have this special familial type. The present HP rate of infection studied with bacterial culture, though similar to that found in other Chinese studies, was lower than in many reports.[22,23] HP infection has been known to induce higher serum gastrin levels and peak acid output capacity among DU patients.[24] Furthermore, mean serum PGI levels are higher among HP-positive controls than these with negative colonisation.[25] In isolated rabbit gastric glands, HP colonisation stimulates pepsinogen secretion.[26] In contrast, acute HP infection even results in hypochlorhydria.[7] We are unable to show an association between HP infection and serum PGI level. There also appears to be no relationship between HP, acid secretion and serum gastrin level.[27] The interaction between HP infection, host, acidity and DU remains controversial.

In summary, the present study confirms the presence of hyperpepsinogenaemia I in DU patients, despite marked overlapping with healthy controls. Many factors which are related to the DU pathogenesis do not necessarily affect serum PGI levels. As a result, DU may be considered a multifactorial and heterogeneous condition.

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