Etiopathogenesis of Gastric Ulcer in Liver Cirrhosis

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Introduction

Liver cirrhosis is frequently complicated by gastric ulceration and many studies have been published regarding the mechanism of this association. The major factors possibly responsible include the influence of hepatic dysfunction on the acid and pepsin contents of gastric juice, insufficient hepatic inactivation of gastric juice secretion stimulating factors, reduced resistance of the gastric mucosa due to malnutrition, disturbed gastric mucosal circulation due to elevated portal pressure, and interactions between gastrointestinal hormones. The exact mechanism is still unclear. In a previous paper, we reported on the high incidence of gastric ulcer in patients with liver cirrhosis¹⁾. This time the relationship between liver cirrhosis and gastric ulceration was investigated by determining the kinetics of gastric juice secretion, the levels of gastrointestinal hormones, the condition of the gastric mucosa, the site of gastric ulceration, and the presence of esophageal varices. In addition, histopathological changes of gastric wall vessels, particularly arteriosclerosis and venosclerosis of the gastric wall, were investigated in autopsy cases.

Subjects and Methods

1. Clinical study

The subjects comprised 30 healthy controls, 49 patients with liver cirrhosis which included 27 with uncomplicated liver cirrhosis (LC) and 22 with liver cirrhosis plus gastric ulcer (LC+GU), and 29 patients with uncomplicated gastric ulcers (GU) (**Table 1**). For assessment of the kinetics of gastric juice secretion, the acid and pepsin levels in gastric juice were examined. Stimulation of gastric juice secretion was performed by the intramuscular injection of 4 μ g/kg tetragastrin. Acid levels were determined according to the method proposed by the Gastric Juice Assay Committee of the Japanese Society of Gastroenterology²⁾. Pepsin activity was determined according to the protocol proposed by the same committee³⁾. Serum gastrin, secretin, and pepsinogen I levels were determined from blood samples taken immedia-

Table 1. Subjects

	Age (years)						Total
	21—40		41—60		61—80		
	Male	Female	Male	Female	Male	Female	
Healthy controls	5	4	7	5	4	5	30
Liver cirrhosis without gastric ulcer	5	2	8	3	7	2	27
Liver cirrhosis with gastric ulcer	4	2	8	2	5	1	22
Gastric ulcer	5	3	6	4	7	4	29

tely before the fasting gastric juice test was performed. Gastrin was determined by radioimmunoassay using Dainabot kit, secretin was determined using a Daiichi Radioisotope kit, and pepsinogen I was determined with a CIS kit. For examination of the gastric mucosa, dye endoscopy (Congo red test) was performed during stimulation by the intramuscular injection of tetragastrin (5 $\mu\text{g/kg}$ body weight). In this examination, the glandular border which distinguishes the acid-secreting region (region of color change) from the non acid secreting region (region without color change) was classified according to the method of Miki et al.⁴⁾. Elevation of the border implies enlargement of the non acid secreting region, i.e., enlargement of the area of gastric mucosa affected by atrophic change. In addition, the mucosa of the antrum, the gastric angle, and the lower, middle and upper gastric bodies were biopsied at endoscopy to determine its background condition particularly the presence or absence of atrophic change. The degree of atrophic change of the mucosa was rated according to the 4-step scale (from normal to severe) of Iida et al.⁵⁾ Endoscopy was performed in order to observe the presence or absence of redness. To eliminate the influence of age, the site of ulceration was compared between respective age groups of the LC+GU and GU groups. In addition, the presence or absence of esophageal varices and their severity were compared between the cirrhotic patients with and without gastric ulcers, using a proposed staging method⁶⁾.

2. Pathological study

The stomachs of the following patients were pathologically examined at autopsy: 47 cases in which liver cirrhosis was evident from autopsy findings, and 26 controls in which no histological changes of the liver were shown at autopsy (Table 2). In each case, 16 specimens of the stomach (from the lesser curvature, greater curvature, anterior and posterior walls of the antrum, middle and upper gastric bodies, and fornix) were prepared

Table 2. Autopsied subjects

	Age (years)				Total
	—60		60—		
	Male	Female	Male	Female	
Controls	6	5	8	7	26
Liver cirrhosis without gastric ulcer	8	3	8	6	25
Liver cirrhosis with gastric ulcer	7	2	9	4	22

and stained with the Elastica van Gieson stain, Weigert's elastica, Azan-Mallory stain, periodic acid-Schiff-alcian blue stain, hematoxylin and eosin stain, and silver stain. Three arteries and veins in the submucosal layer were selected at random for assessment of vessel wall sclerosis according to the classifications of Kawamura et al.⁷⁾, (**Table 3**) and Arai⁸⁾, (**Table 4**), respectively. The degree of sclerosis was compared between patients above and below 60 years of age in each of the groups. Statistical significance of differences was evaluated using Student's t-test, and $P < 0.05$ was regarded as statistically significant.

Table 3. Classification of arteriosclerosis in the gastric wall

0 : No change
1 : Thickening of the endothelium is seen around less than 1/10 of the vessel.
2 : Thickening of the endothelium is seen around part of the vessel.
3 : Thickening of the endothelium is circumferential.
4 : The endothelium is partially the same thickness as the mesothelium.
5 : The endothelium is the same thickness as the mesothelium.
6 : The endothelium is wider than the mesothelium.
7 : There is calcification or advanced stenosis of the lumen.

Table 4. Classification of venosclerosis in the gastric wall

0 : No change
1 : There is partial cellular intimal thickening.
2 : Cellular intimal thickening is circumferential.
3 : There is partial cellular/fibrous intimal thickening.
4 : Cellular/fibrous intimal thickening is circumferential.
5 : There is partial fibrous intimal thickening.
6 : Fibrous intimal thickening is circumferential.
7 : The wall is thinned due to variceal distension in addition to the above.

Results

1. Clinical study

1.1. Kinetics of gastric juice secretion

Basal acid output (BAO) (Fig. 1)

The BAO was 1.87 ± 0.95 mEq/hr in healthy controls, 0.80 ± 0.35 mEq/hr in LC group, 1.06 ± 0.73 mEq/hr in LC+GU group, and 1.74 ± 0.95 mEq/hr in GU group. Thus, the BAO values in LC and LC+GU groups were significantly lower than in GU group and healthy controls ($P < 0.01$). The BAO in LC+GU group was not significantly higher than in LC group.

Maximal acid output (MAO) (Fig. 1)

The MAO was 10.26 ± 2.35 mEq/hr in healthy controls, 6.26 ± 3.14 mEq/hr in LC group, 8.16 ± 3.43 mEq/hr in LC+GU group, and 8.97 ± 3.27 mEq/hr in GU group. Thus, the MAO in LC group was significantly lower than in healthy controls and GU group ($P < 0.01$), and the MAO in LC+GU group was significantly lower than in healthy controls ($P < 0.01$). The MAO in LC+GU group was not significantly higher than in LC group.

Fig. 1. Gastric acid output

Normal, Healthy controls ; LC, Liver cirrhosis without gastric ulcer ;
 LC+GU, Liver cirrhosis with gastric ulcer ; GU, Gastric ulcer
 Basal acid output (▨ BAO), Maximal acid output (□ MAO)

Fig. 2. Pepsin output

Normal, Healthy controls ; LC, Liver cirrhosis without gastric ulcer ;

LC+GU, Liver cirrhosis with gastric ulcer ; GU, Gastric ulcer

Basal pepsin output (■ BPO), Stimulated pepsin output (□ SPO).

Basal pepsin output (BPO) (Fig. 2)

The BPO was 55.73 ± 15.72mg of tyrosine/hr in healthy controls, 30.72 ± 12.32mg of tyrosine/hr in LC, 34.77 ± 14.76mg of tyrosine/hr in LC+GU, and 49.27 ± 23.01mg of tyrosine/hr in GU. The BPO values in LC and LC+GU groups were significantly lower than in healthy controls and GU group ($P < 0.01$). The BPO in LC+GU group was not significantly higher than in LC group.

Stimulated pepsin output (SPO) (Fig. 2)

The SPO was 146.70 ± 41.53mg of tyrosine/hr in healthy controls, 88.18 ± 39.16mg of tyrosine/hr in LC, 105.60 ± 33.51mg of tyrosine/hr in LC+GU, and 129.84 ± 55.98mg of tyrosine/hr in GU. The SPO values in LC and LC+GU groups were significantly lower than those in healthy controls ($P < 0.01$), and SPO in LC+GU group was significantly lower than in GU group ($P < 0.05$). The SPO in LC+GU group was not significantly higher than in LC group.

1.2. Gastrointestinal hormones

Fasting serum gastrin (FSG) (Fig. 3)

The FSG level was 93.17 ± 21.73 pg/ml in healthy controls, 83.23 ± 42.27 pg/ml in LC

group, 99.70 ± 30.71 pg/ml in LC+GU group, and 90.28 ± 39.23 pg/ml in GU group. No significant difference was observed between LC and LC+GU groups.

Fasting serum secretin (FSS) (Fig. 3)

The FSS level was 107.17 ± 20.94 pg/ml in healthy controls, 123.04 ± 27.90 pg/ml in LC, 114.98 ± 23.21 pg/ml in LC+GU, and 121.41 ± 45.77 pg/ml in GU. No significant difference was observed between LC and LC+GU groups.

1.3. Fasting serum pepsinogen I

Fasting serum pepsinogen I (PGI) (Fig. 3)

The PGI level was 80.68 ± 25.03 ng/ml in healthy controls, 63.36 ± 25.48 ng/ml in LC, 67.74 ± 14.22 ng/ml in LC+GU, and 79.83 ± 22.45 ng/ml in GU. The PGI levels in LC and LC+GU groups were significantly lower than in healthy controls and GU group ($P < 0.05$), although this parameter did not significantly differ between LC and LC+GU groups.

Fig. 3. Fasting serum gastrin (■ FSG), fasting serum secretin (□ FSS) and fasting serum pepsinogen I (▨ PGI) levels. Normal, Healthy controls; LC, Liver cirrhosis without gastric ulcer; LC+GU, Liver cirrhosis with gastric ulcer; GU, Gastric ulcer.

1.4. Gastric mucosa

Glandular border examination by the Congo red test (Table 5)

The glandular border was classified into the closed type (C₀-C₂) and the open type (O₁-O₃). The level of the glandular border in LC and LC+GU groups tended to be higher than in healthy controls and GU group at all ages.

Endoscopic appearance of the mucosa (Table 6)

Table 5. Appearance of the glandular border in the endoscopic congo red test

	Age (years)											
	21 — 40						41 — 60					
	Closed type			Open type			Closed type			Open type		
	C ₀	C ₁	C ₂	O ₁	O ₂	O ₃	C ₀	C ₁	C ₂	O ₁	O ₂	O ₃
Healthy controls	4	3	1	1	0	0	1	5	2	2	2	0
Liver cirrhosis without gastric ulcer	1	2	2	1	1	0	2	1	3	3	2	1
Liver cirrhosis with gastric ulcer	1	1	1	2	1	0	1	2	2	2	2	1
Gastric ulcer	2	3	2	1	0	0	2	4	1	1	1	1

Table 6. Gastric mucosal atrophy and erythema in the four groups

	Age (years)	No. of patients	Atrophic change				Erythema	
			(-)	(+)	(++)	(###)	(-)	(+)
Healthy controls	21 — 40	9	6	3			8	1
	41 — 60	12	6	5	1		11	1
	61 — 80	9	3	4	2		7	2
Liver cirrhosis without gastric ulcer	21 — 40	7	3	3		1	4	3
	41 — 60	11	2	4	3	2	5	6
	61 — 80	9	1	3	4	1	3	6
Liver cirrhosis with gastric ulcer	21 — 40	6	1	2	2	1	2	4
	41 — 60	10	1	3	4	2	4	6
	61 — 80	6	1	2	1	2	1	5
Gastric ulcer	21 — 40	8	4	3	1		6	2
	41 — 60	10	4	3	2	1	8	2
	61 — 80	11	3	5	2	1	8	3

Atrophic change and redness tended to be more frequent in LC and LC+GU groups than in healthy controls and GU group.

Site of ulceration

As shown in Fig. 4, GU and LC+GU groups frequently had ulcers in the gastric angle and lesser curvature at all ages.

Fig. 4. Locations of gastric ulcers in patients with liver cirrhosis with gastric ulcer and gastric ulcer alone by age and sex.

A.W., anterior wall; L.C., lesser curvature; P.W., posterior wall; G.C. greater curvature; U.B. upper body; M.B., middle body; L.B., lower body; Ang, angle; Ant, antrum; Prepy, prepylorus.

Table 7. Clinical stage of esophageal varices in liver cirrhotic patients with and without gastric ulcer

Group	No. of patients with varices	Stage											
		I			II			III			IV		
		Age (years)			Age (years)			Age (years)			Age (years)		
		21	41	61	21	41	61	21	41	61	21	41	61
Liver cirrhosis without gastric ulcer	11	40	60	80	40	60	80	40	60	80	40	60	80
		1	3	2	0	1	2	0	1	1	0	0	0
Liver cirrhosis with gastric ulcer	14	40	60	80	40	60	80	40	60	80	40	60	80
		1	3	1	1	2	2	1	2	1	0	0	0

1.5. Esophageal varices in the liver cirrhosis without gastric ulcer and liver cirrhosis with gastric ulcer.

As shown in Table 7, the presence of esophageal varices was more frequent in LC+GU group than in LC group. In LC+GU patients with esophageal varices, the varices were often severe i.e., Stage III where the red color sign is visible.

2. Pathological study

2.1. Arteriosclerosis

As shown in Fig. 5, the arteriosclerotic index (A.I.) of the antrum in patients aged over 60 was significantly lower in cirrhotic patients with gastric ulcer (1.38 ± 0.62) and without gastric ulcer (0.99 ± 0.60) than those of controls (2.36 ± 0.67) ($P < 0.01$). The A.I. of the body in patients aged over 60, was significantly lower in both LC with GU group (1.36 ± 0.61) and LC without GU group (1.21 ± 0.51) than those of Control group (2.74 ± 0.72) ($P < 0.01$). In the fornix aged over 60, the index was significantly lower in both LC+GU group (1.66 ± 0.69) and LC group (1.67 ± 0.63) than in Control group (3.39 ± 0.81) ($P < 0.01$).

In controls aged over 60, the A.I. was significantly lower in the antrum (2.36 ± 0.67) than in the fornix (3.39 ± 0.81) ($P < 0.01$), as shown in Fig. 5. In uncomplicated cirrhotic patients aged over 60, the index in the antrum (0.99 ± 0.60) was also significantly lower than that in the fornix (1.67 ± 0.63) ($P < 0.05$).

2.2. Venosclerosis

As shown in Fig. 6, in the antrum of patients aged under 60, the venosclerotic index (V.I.) was significantly higher in both cirrhotic patients with (4.38 ± 0.66) and without gastric ulcer (4.26 ± 0.75) than in controls (1.60 ± 0.66) ($P < 0.001$). In the body of patients aged under 60, the V.I. was significantly higher in both LC with GU group (4.80 ± 0.77) and LC without GU group (4.69 ± 0.70) than in Control group (1.04 ± 0.90) ($P < 0.001$).

In the fornix of patients aged under 60, the index was significantly higher in both LC with GU group (5.39 ± 0.78) and LC without GU group (5.12 ± 0.91) than in Control group (1.98 ± 0.93) ($P < 0.001$). In the antrum of patients aged over 60, the V.I. was significantly higher in both cirrhotic patients with gastric ulcer (4.24 ± 0.78) and without gastric ulcer (4.21 ± 0.66) than in controls (1.86 ± 0.80) ($P < 0.001$). In the body of patients aged over 60, the V.I. was significantly higher in both LC with GU group (4.64 ± 0.73) and LC without GU group (4.36 ± 1.01) than in Control group (1.71 ± 0.74) ($P < 0.001$). In the fornix of patients aged over 60, the index was significantly higher in both LC with GU group (5.01 ± 0.91) and LC without GU group (4.77 ± 0.90) than in Control group (2.07 ± 0.98) ($P < 0.001$).

As shown in Fig. 6, in cirrhotic patients with gastric ulcer aged under 60, the V.I.

Fig. 5. Degree of arteriosclerosis at various gastric locations related to age.
 LC with GU, liver cirrhosis with gastric ulcer ; LC without GU, liver cirrhosis without gastric ulcer

Fig. 6. Degree of venosclerosis at various gastric locations related to age.
 LC with GU, liver cirrhosis with gastric ulcer ; LC without GU, liver cirrhosis without gastric ulcer.

in the fornix (5.39 ± 0.78) was significantly higher than in the antrum (4.38 ± 0.68) ($P < 0.05$). In uncomplicated cirrhosis cases aged under 60, the V.I. in the fornix (5.12 ± 0.91) was also significantly higher than in the antrum (4.26 ± 0.75) ($P < 0.05$). In the cases aged over 60, the index was significantly higher in the fornix (5.01 ± 0.91 for LC+GU group and 4.77 ± 0.90 for LC group) than in the antrum (4.21 ± 0.78 for LC+GU group and 4.21 ± 0.66 for LC group) ($P < 0.05$).

Discussion

1) Ulcerogenic factors

The association between liver cirrhosis and gastric ulcer was first investigated in this study from the aspect of ulcerogenic factors. Reports on the level of acid secretion in cirrhosis have differed widely. Some investigators have reported reduced acid secretion⁹⁾, while others have reported a slight reduction^{10) 11)}, a slight elevation¹²⁾ or a distinct elevation¹³⁾. When acid secretion was compared between cirrhotic patients with and without gastric ulcer, those with gastric ulcer showed either a significant increase^{10) 14)} or a tendency for an increase^{11) 15)} in acid secretion. In the present study, basal acid output and maximal acid output were found to be significantly lower in cirrhotic patients both with and without gastric ulcer than in healthy controls. The absence of a significant difference in acid secretion between cirrhotic patients with and without gastric ulcer indicates that acid secretion is probably not directly involved in the onset of gastric ulcer in cirrhosis.

Many previous studies have reported a reduction of pepsin output in the gastric juice of patients with liver cirrhosis^{14) 16)}. Also in the present study, the basal and stimulated pepsin outputs were significantly lower in cirrhotic patients with and without gastric ulcer than in healthy controls. However, neither the basal nor the stimulated pepsin output was significantly different between the cirrhotic patients with and without gastric ulcer, suggesting that pepsin output in gastric juice is also not directly involved in gastric ulcer production in cirrhosis.

Some investigators have reported that the serum gastrin level is elevated in patients with liver cirrhosis^{13) 17)} due to impaired hepatic inactivation of gastrin. However, many other authors have disputed the idea of hepatic inactivation of gastrin^{18) 19)}, and it is more widely accepted that it is broken down by the kidney²⁰⁾. The investigators who observed elevated blood gastrin levels in cirrhosis claimed the involvement of a feedback mechanism related to hypoacidity of the gastric juice, although others have not accepted such an idea⁹⁾. Some authors have suggested that both secretion and gastrin formation are reduced in cirrhosis to cause a fall in the serum gastrin level¹²⁾, although there is a study reporting no difference

in serum gastrin levels between patients with cirrhosis and healthy individuals¹⁵⁾. In the present study, serum gastrin was found not to significantly differ between patients with cirrhosis with or without gastric ulcers and healthy controls, suggesting that the serum gastrin level was not directly involved in the development of gastric ulcers in cirrhosis.

Serum secretin levels have been reported to be high in cirrhosis in some studies^{21) 22)}, but no significant difference has been found between cirrhosis and healthy controls in other studies^{9) 11)}. In the present study, serum secretin levels did not significantly differ between patients with cirrhosis with or without gastric ulcers and healthy controls. Therefore, it is unlikely that serum secretin plays an important role in the development of gastric ulcer in cirrhosis. Pepsinogen I levels were reported by Adachi¹⁶⁾ to be significantly lower in cirrhotic patients than in healthy individuals. In the present study, cirrhotic patients with and without gastric ulcer also showed a significant reduction in serum pepsinogen I levels compared to healthy controls. However, the levels were not significantly different between cirrhotic patients with and without gastric ulcers, suggesting that changes in serum pepsinogen I levels are also unlikely to be involved in the development of gastric ulceration in cirrhosis.

2) Defensive factors

Further discussion of this issue involves the aspect of defensive factors. In the present study, I visualized the glandular border using the endoscopic Congo red test, which allows sensitive and simple assessment of the acid-secreting area and the area of atrophic mucosa. According to some investigators, the closed type is rare and the open type is frequent in cirrhosis, indicating the progression of atrophy of the fundic glands²³⁾. In the present study, the glandular border tended to be located higher in cirrhotic patients with and without gastric ulcer as compared to healthy controls and patients with gastric ulcer alone.

When the background condition of the mucosa was investigated, cirrhotic patients with and without gastric ulcer showed atrophic changes and intestinal metaplasia. This was frequently accompanied by redness. A high incidence of atrophic gastritis in cirrhosis was also found in our previous study¹⁾. The mucosal redness of the gastric body represents congestion and is caused by marked dilatation of capillaries due to elevated portal pressure¹⁶⁾. These results suggest that defensive functions are reduced in the gastric mucosa in cirrhosis.

The site of gastric ulceration in cirrhosis differs from report to report. Some investigators have stated that the site is often the gastric angle¹¹⁾, while others have reported that it is frequently the midsection of the gastric body and sometimes the upper gastric body¹⁵⁾. In the present study, gastric ulcer was most frequently found in the gastric angle, and it was more frequently seen in the body than in the antrum.

3) Presence of esophageal varices

Regarding the association between esophageal varices and gastric ulcer in cirrhosis, Fukumoto et al.²⁴⁾ have reported that the incidence of gastric ulcer was higher in cirrhotic patients with varices and that the incidence increased as the varices became more severe. Matsui et al.¹¹⁾ also reported that the incidence of gastric ulcer tended to increase as esophageal varices became more severe. They attributed this to regional congestion, i.e., the circulatory disturbances due to portal hypertension were seen as a major factor in the onset of gastric ulcer and acid was seen as a secondary factor which affects the weakened mucosa. In addition, Fukuda et al.²⁵⁾ have reported that the portal pressure tends to be higher in cirrhotic patients with gastric ulcer than in uncomplicated cirrhosis, and that the incidence of gastric ulcer was higher in cirrhotic patients with esophageal varices. They speculated that the mucosal lesions which occurred as esophageal varices became more severe were attributable to regional disturbances of gastric mucosal circulation due to portal hypertension. The present study also showed that the incidence of gastric ulceration tended to increase in parallel with the severity of the esophageal varices.

4) Sclerosis of the blood vessels

A pathological study of the degree of arteriosclerosis by Atari²⁶⁾ showed that arteriosclerosis of the stomach was more frequent and more severe in the region of the left gastric artery than in the pyloric glandular region supplied by the right gastric artery. In the present pathological autopsy study, controls aged over 60 years had more marked arteriosclerosis in the fornix than in the antrum, supporting the reports of Kawamura⁷⁾ and Atari²⁶⁾. Regarding gastric wall arteriosclerosis and cirrhosis, it has been reported that arterial lesions are remarkably mild in cirrhotic patients with gastric ulcers²⁷⁾. In the present study, the degree of arteriosclerosis in the antrum, gastric body, and fornix was significantly lower in cirrhotic patients both with and without gastric ulcers aged over 60 years than in controls of the same age group ($P < 0.01$), although no significant difference was noted at ages below 60 years. Regarding venosclerosis, Shizawa et al.²⁸⁾ performed a histological study of stomachs removed from cirrhotic patients with gastric ulcers, and found that dilatation of the gastric wall veins and hypertrophy of the intima were already marked in the early stages of cirrhosis. This suggested the involvement of disturbed gastric mucosal circulation in ulceration even from the early stages of cirrhosis. Watanabe²⁹⁾ has attributed the onset of mucosal lesions to the weakening of mucosal defensive functions by disturbances of the gastric mucosal circulation (venous congestion). Such changes are gradually caused by the development of gastric mucosal venosclerosis following congestion in the portal region due to portal hypertension. Venous lesions of the gastric wall in cirrhosis are claimed to be more

severe in patients with gastric ulcers than in those without them²⁷⁾. In the present study, the degree of venosclerosis was significantly higher in cirrhotic patients both with and without gastric ulcers than in controls. However, because it did not significantly differ between cirrhotic patients with and without gastric ulcers, it seems impossible to explain the development of gastric ulceration based on venosclerosis alone.

In the past, the onset of gastric ulcer in cirrhosis has been studied mainly from the aspect of gastric mucosal blood flow, but no previous study has assessed the degree of gastric mucosal arteriosclerosis and venosclerosis in determining the role of gastric mucosal blood flow in the onset of gastric ulceration. Particular attention was paid to this point in designing the present study.

5) Proposed mechanism of induction of gastric ulceration in liver cirrhosis

The results of the present study suggested the following mechanism for the development of gastric lesions in liver cirrhosis. First, venous dilatation of the gastric wall and hypertrophy of the intima occur due to portal hypertension, and are followed by worsening of gastric wall venosclerosis. As a result, congestion and circulatory disturbances occur, that lead to weakening of the mucosa, i.e., a reduction of its defensive functions. Accordingly, the balance between ulcerogenic and defensive factors is lost, and this leads to the development of gastric lesions.

Summary

The mechanism of the complication of liver cirrhosis by gastric ulcer was studied from various aspects, including the kinetics of gastric juice secretion, gastrointestinal hormones, fasting serum pepsinogen I, the condition of the gastric mucosa, the site of gastric ulceration, and the presence of esophageal varices. In addition, it was histopathologically studied by examining arteriosclerosis and venosclerosis of the gastric wall in autopsy cases. Both the basal and stimulated acid and pepsin outputs were significantly lower in cirrhotic patients with and without gastric ulcers than in healthy controls ($P < 0.01$). Fasting serum gastrin and secretin did not significantly differ between cirrhotic patients and healthy controls. Fasting serum pepsinogen I in cirrhotic patients was significantly lower than in healthy controls ($P < 0.05$). The level of the glandular border in cirrhotic patients tended to be higher than in healthy controls and the gastric ulcers at all age groups. Endoscopic observation of the mucosa showed that normal mucosa was uncommon in cirrhotic patients both with and without gastric ulcers. In these patients, atrophic changes and erythema were frequent. Both gastric ulcer patients and cirrhotic patients with gastric ulcers frequently had ulcers in the gastric angle and lesser curvature at all ages. The incidence and severity of esophageal varices tended to be higher in cirrhotic patients with gastric

ulcers than in those without gastric ulcers. The red color sign was positive in many of the cases complicated by gastric ulcer. The degree of arteriosclerosis in the antrum, gastric body, and fornix was significantly lower in cirrhotic patients both with and without gastric ulcers aged over 60 years than in controls of the same age group ($P < 0.01$). The degree of venosclerosis of the antrum, gastric body and fornix was significantly higher in cirrhotic patients both with and without gastric ulcers than in controls aged under and over 60 ($P < 0.001$). In cirrhotic patients with and without gastric ulcer aged under and over 60, the venosclerotic index in the fornix was significantly higher than in the antrum ($P < 0.05$).

The results of the present study suggested that venous congestion and circulatory disturbances occur by gastric wall venosclerosis due to portal hypertension, and lead to weakening of the mucosa, i.e., a reduction of its defensive functions. Accordingly, the balance between ulcerogenic and defensive factors is lost, and this leads to the development of gastric lesions.

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