Mechanisms of gastric emptying disturbances in chronic and acute inflammation of the distal gastrointestinal tract

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Keller J, Beglinger C, Holst JJ, Andresen V, Layer P. Mechanisms of gastric emptying disturbances in chronic and acute inflammation of the distal gastrointestinal tract. Am J Physiol Gastrointest Liver Physiol 297: G861–G868, 2009. First published August 27, 2009; doi:10.1152/ajpgi.00145.2009.—It is unclear why patients with inflammation of the distal bowel complain of symptoms referable to the upper gastrointestinal tract, specifically to gastric emptying (GE) disturbances. Thus we aimed to determine occurrence and putative pathomechanisms of gastric motor disorders in such patients. Thirteen healthy subjects (CON), 13 patients with Crohn’s disease (CD), 10 with ulcerative colitis (UC), and 7 with diverticulitis (DIV) underwent a standardized 13C-octanoic acid gastric emptying breath test. Plasma glucose, CCK, peptide YY, and glucagon-like peptide-1 (GLP-1) were measured periodically and correlated with GE parameters. Results were given in means ± SD. Compared with CON, GE half time (T1/2) was prolonged by 50% in CD (115 ± 55 vs. 182 ± 95 min, P = 0.037). Six CD, 2 DIV, and 2 UC patients had pathological T1/2 (>200 min). Postprandial plasma glucose was increased in all patients but was highest in DIV and correlated with T1/2 (r = 0.90, P = 0.006). In CD, mean postprandial CCK levels were increased threefold compared with CON (6.5 ± 6.7 vs. 2.1 ± 0.6 pmol/l, P = 0.027) and were correlated with T1/2 (r = 0.60, P = 0.041). Compared with CON, GLP-1 levels were increased in UC (25.1 ± 5.2 vs. 33.5 ± 13.0 pmol/l, P = 0.046) but markedly decreased in DIV (9.6 ± 5.2 pmol/l, P < 0.0001). We concluded that a subset of patients with CD, UC, or DIV has delayed GE. GE disturbances are most pronounced in CD and might partly be caused by excessive CCK release. In DIV there might be a pathophysiological link between decreased GLP-1 release, postprandial hyperglycemia, and delayed GE. These explorative data encourage further studies in larger patient groups.

inflammatory bowel disease; diverticulitis; motility; hormonal regulation

UPPER GASTROINTESTINAL SYMPTOMS such as nausea, vomiting, and anorexia are common in patients with lower gastrointestinal tract disease such as Crohn’s disease (CD), ulcerative colitis (UC), or diverticulitis (DIV), but mechanisms have not been elucidated.

Conceivably, gastric emptying disturbances might play a pathophysiological role, but only few studies have addressed gastric motility in inflammatory bowel disease (IBD) and virtually none in diverticulitis. Available data suggest delayed gastric emptying of solids in subgroups of patients with CD (2, 19, 20) and UC (47, 50).

Several hypothetical pathomechanisms have been discussed. First, gastrointestinal obstruction in CD may cause delayed gastric emptying but does not explain the findings sufficiently (2). Second, hyperglycemia is associated with delayed gastric emptying (15, 37, 53), and, hence, increased blood glucose levels might cause gastric dysmotility in IBD patients receiving corticosteroid therapy. Third, autonomic neuropathy (10, 16, 54) and alterations of intramural neurons (9, 28, 40, 45) have been observed in IBD and might disturb gastrointestinal motility. Finally, there is evidence that release of several gastrointestinal neurohormonal mediators that regulate gastric functions may be altered in IBD (1, 7, 49, 58, 59); however, these results were conflicting, and roles of key regulators, particularly CCK, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1) (51) have remained unclear. Disturbed release of gastrointestinal hormones from the inflamed mucosa might also contribute to gastric emptying disturbances in diverticulitis, but no systematic studies have been reported.

In an exploratory study, we aimed to determine whether gastric emptying is delayed in patients with distal gastrointestinal inflammation and, if yes, whether these disturbances might be explained by altered blood glucose or release of humoral regulators of gastric motility. Thus we compared gastric emptying of a standardized test meal, postprandial blood glucose control, and release of relevant humoral mediators in healthy subjects and in patients with CD, UC, or diverticulitis.

MATERIALS AND METHODS

Human Subjects and Setting

The protocol was approved by the ethics committee of the Hamburg Medical Association. After giving informed written consent, 13 healthy subjects (5 females, age: 26.7 ± 4.3 yr, BMI: 23.1 ± 3.1 kg/m²), 10 patients with UC, 13 patients with CD, and 7 with diverticulitis participated. The clinical part of the study was performed at the Israelitic Hospital in Hamburg.

IBD patients. Thirty patients (10 females) with CD and 10 with UC (4 females) and presently no or only moderate disease activity participated in the study. We excluded patients with evidence of upper gastrointestinal obstruction, impaired liver or lung function, or diabetes mellitus. Patient characteristics are given in table 1. In one female UC patient (49 years), clinical data were insufficient to score disease activity and extension.

Diverticulitis patients. All patients (n = 7, 4 females, age: 67.7 ± 5.2 yr, BMI: 26.9 ± 3.2 kg/m²) had documented diverticulitis affecting the sigmoid colon and were receiving intravenous antibiotics. However, only patients who had partially recovered and were allowed to ingest solid foods participated, whereas patients who had a history or previous evidence of diabetes or received corticosteroids or ongoing parental nutrition were excluded. Mean C-reactive protein (CRP) investigated within 24 h of the gastric emptying test was 30 ± 13 mg/l.

Performance and Reliability of Gastric Emptying Test

A standardized 13C-octanoic acid breath (13C-OABT) test was performed in all subjects. The test meal consisted of an omelet (1 egg, yolk doped with 91 mg 13C-octanoic acid, purchased from Eurisotop,
that the $^{13}$C-OABT reliably reflected gastric emptying of solids in our histological lesions in two patients with CD (Table 1), we conclude of the proximal gastrointestinal tract apart from small ulcers and/or

25) is irrelevant. Because we did not have evidence for involvement patients with subacute diverticulitis, there is no evidence of impaired severe malabsorption or severe liver or lung disease. In our patients, the available mathematical equations (18, 34). Instead, both parameters ulcerative colitis; CIA, Clinical Activity Index.

| Colonic involvement scores are as follows: 1 = proctitis, 2 = rectosigmoiditis, 3 = left sided colitis, 4 = subtotal colitis, and 5 = pancolitis. *Colectomized, f= resection of ileocecal region. E, esophageal; G, gastric; J, jejunal; I, ileal; C, colonic involvement. CD, Crohn’s disease; CDAI, CD Activity Index; UC, ulcerative colitis; CIA, Clinical Activity Index.

Saarbruecken, Germany), 50 g ham, 2 slices of white bread, 10 g butter, and 200 ml orange juice (13, 24). Breath samples were obtained before ingestion of the meal, at 15-min intervals up to 240 min and 270 and 300 min postprandially. The $^{13}$C/$^{12}$C ratio was obtained before ingestion of the meal, at 15-min intervals up to 240 min and 270 and 300 min postprandially. The $^{13}$C-OABT reliably reflected gastric emptying of solids in our patients. Observation period so that T1⁄2 and T lag could not be quantified by the available mathematical equations (18, 34). Instead, both parameters were estimated to be at least as long as the observation period (300 min).

Reliability of the $^{13}$C-OABT may be impaired in patients with severe malabsorption or severe liver or lung disease. In our patients, the latter were excluded by clinical and laboratory examinations. In patients with subacute diverticulitis, there is no evidence of impaired nutrient absorption. Octanoic acid is absorbed without further requirements as soon as it enters the duodenum. As a consequence, potentially decreased pancreatic exocrine function as observed in IBD (22, 25) is irrelevant. Because we did not have evidence for involvement of the proximal gastrointestinal tract apart from small ulcers and/or histological lesions in two patients with CD (Table 1), we conclude that the $^{13}$C-OABT reliably reflected gastric emptying of solids in our patients.

Hormone and Blood Glucose Concentrations

Venous blood samples were obtained before, at 15-min intervals during the first 60 min, 30-min intervals up to 240 min, and at 300 min postprandially for measurement of blood glucose, PY, GLP-1, and CCK plasma levels as has been described in detail before (12, 38, 44, 52). Detection limits of all radioimmunoassays were below 2 pmol/l. For CCK, hormone concentrations above 25 pmol/l could not be further evaluated because of a lack of additional plasma. Blood samples were available for all healthy volunteers, all patients with UC or diverticulitis, and for 12 CD patients.

Definitions

The early postprandial period was defined as the first half of the 300-min observation period, the late postprandial period as the second half. Postprandial hormone release was defined as increase over basal, i.e., fasting levels. To test for effects of disease localization, patients with CD were divided into four patients with exclusively ileal involvement and nine patients with colonic affection with or without additional inflammation of more proximal sites (Table 1). Extension of disease in UC patients was scored as: 1 = proctitis, 2 = rectosigmoiditis, 3 = left sided colitis, 4 = subtotal colitis, 5 = pancolitis (Table 1). Disease severity was estimated by the CD Activity Index (CDAI) (8), the Clinical Activity Index (CAI) for UC (46), and/or CRP levels.

Statistics

Statistical analyses were considered as exploratory. We used the respective Student’s t-test for paired comparisons. ANOVA was used for statistical analysis of differences between healthy controls and individual patient groups. Because of the limited number of subjects per group we did not test for statistical significance of and generally did not describe differences between patient groups. Moreover, we used linear regression analysis with calculation of the Pearson correlation coefficient where appropriate. Data are given as means ± SD unless stated otherwise. P ≤ 0.05 was regarded as statistically significant; because of the exploratory nature of the study trends were described if P ≤ 0.10 (11). Statistical analyses were performed using Microsoft Excel, version 11.5.0 and JMP version 6.0.3 from SAS.

RESULTS

Gastric Emptying

For postprandial $^{13}$C-exhalation over time no significant differences were observed between healthy controls and any of the patient groups (Fig. 1A). T1⁄2 and T lag were similar in controls and UC but significantly increased by about 50% in CD (P ≤ 0.044 vs. controls). T1⁄2 tended to be prolonged in diverticulitis patients (Fig. 1B, P = 0.10 vs. controls). According to our normal values T1⁄2 was pathologically prolonged (>200 min) in six individuals with CD, two with UC, and two with diverticulitis (Fig. 3).

Blood Glucose

Compared with healthy volunteers, fasting plasma glucose concentrations tended to be increased in diverticulitis, only (4.57 ± 0.56 vs. 5.04 ± 0.50 mmol/l, P = 0.083). Postprandially, plasma glucose increased significantly in all groups (P < 0.0005; Fig. 2A), but mean postprandial plasma glucose was significantly higher in CD (5.45 ± 0.78) and UC (5.40 ± 0.62 mmol/l) compared with controls (4.59 ± 0.47 mmol/l, P = 0.003 and P = 0.002, respectively) and highest in diverticulitis (6.23 ± 0.45 mmol/l, P < 0.0001 vs. controls). Individual values for maximal postprandial blood glucose concentrations are shown in Fig. 3. We observed no significant correlations between plasma glucose and gastric emptying parameters in controls or IBD. By contrast, in diverticulitis, mean late postprandial plasma glucose concentrations were tightly correlated with T1⁄2 (r = 0.90, P = 0.006) and T lag (r = 0.91, P = 0.005).

Table 1. Clinical characteristics of patients with inflammatory bowel disease

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hormone release tended to be stronger for mean compared with maximal hormone levels.

CCK. Postprandially, CCK plasma levels increased significantly in controls and all patient groups (Fig. 2). They were similar in healthy subjects, patients with UC, and patients with diverticulitis but were markedly and significantly elevated in patients with CD compared with controls throughout the postprandial period (Fig. 2). Moreover, $T_{1/2}$ ($r = 0.60, P = 0.041$) and $T_{lag}$ ($r = 0.61, P = 0.036$) correlated directly with mean CCK plasma concentrations in CD (Fig. 4; please note that, for methodological reasons, neither $T_{1/2} > 300$ min nor CCK concentrations above 25 mmol/l could be quantified exactly). Five out of twelve CD patients in whom hormone plasma levels were available had pathologically prolonged $T_{1/2}$ and $T_{lag}$. Of these, four had markedly elevated CCK plasma levels compared with healthy controls [Fig. 4, upper level of normal obtained from healthy volunteers [means + (2 $\times$ SD)] and indicated by broken line].

PYY. Postprandially, mean PYY plasma levels appeared to be higher in all patient groups compared with healthy controls, but only in diverticulitis these differences reached statistical significance (Fig. 2). Single patients with all types of bowel inflammation had markedly high peak PYY plasma concentrations (>100 pmol/l, Fig. 3). Only in controls mean early postprandial PYY release was directly correlated with $T_{1/2}$ ($r = 0.59, P = 0.035$) and $T_{lag}$ ($r = 0.58, P = 0.037$).

GLP-1. Following ingestion of the test meal, GLP-1 plasma levels increased significantly in all groups compared with basal values ($P < 0.02$, Fig. 2). Compared with controls (25.1 $\pm$ 5.2 pmol/l) mean early postprandial GLP-1 plasma concentrations were significantly higher in UC (33.5 $\pm$ 13.0 pmol/l, $P = 0.046$) and were strongly decreased in diverticulitis (9.6 $\pm$ 5.2 pmol/l, $P < 0.0001$). Postprandial GLP-1 plasma concentrations or release were not associated with gastric emptying parameters in healthy subjects, patients with UC, or patients with diverticulitis. In CD, $T_{1/2}$ ($r = 0.61, P = 0.037$) and $T_{lag}$ ($r = 0.58, P = 0.046$) correlated with mean GLP-1 plasma concentrations late postprandially (Fig. 4).

**Influence of Disease Characteristics**

In UC, activity (CAI and CRP) and extension of disease were not correlated with gastric emptying parameters, blood glucose control, or release of gastrointestinal hormones, whereas steroid dose was directly associated with the postprandial increase in plasma glucose ($r = 0.75, P = 0.020$).

In CD, disease activity (CDAI) and steroid dose were directly associated ($r = 0.80, P = 0.001$), and both parameters correlated with a high increase in plasma glucose concentrations over basal late postprandially (CDAI: $r = 0.72, P = 0.006$; steroid dose: $r = 0.82, P = 0.0006$). Moreover, postprandial PYY plasma concentrations were directly correlated with disease activity (CDAI: $r = 0.74, P = 0.006$; CRP: $r = 0.92, P = 0.0001$). Release of the other hormones or gastric emptying parameters were not associated with disease activity or steroid dose. By contrast, extension of the disease apparently influenced plasma concentrations of CCK and gastric emptying. Mean postprandial CCK plasma concentrations were significantly higher in CD patients with exclusively ileal disease ($n = 4$) compared with those with extensive disease ($n = 9$).
Correspondingly, gastric emptying was significantly prolonged in the former group (Fig. 5).

In diverticulitis patients, CRP levels did not correlate with gastric emptying parameters, plasma glucose, CCK, or PYY. A weak inverse correlation was observed between CRP levels and late postprandial GLP-1 release \((r = -0.70, P = 0.078)\).

**DISCUSSION**

Our findings suggest that gastric emptying disturbances occur in chronic and acute inflammation of the distal gastrointestinal tract. Patients with CD have significantly prolonged gastric emptying half time measured by \(^{13}\)C-OABT compared
with healthy controls. By contrast, there is no significant difference between mean half emptying time in UC or diverticulitis patients compared with controls, but a subset of patients from both groups have pathologically delayed gastric emptying according to our normal values (24).

With regard to patients with IBD, these findings largely concur with literature data (2, 3, 19, 20). Concerning diverticulitis patients, to our knowledge this study is the first to systematically investigate gastric emptying of solids. The lack of previous investigations is probably attributable to the fact that acute diverticulitis patients do not receive oral food, which prevents measurement of gastric emptying. To circumvent this problem, we investigated patients recovering from diverticulitis who still received intravenous antibiotics but in whom solid foods had already been reintroduced. Thus we speculate that an even greater delay of gastric emptying might occur during the early phase of the disease.

Although there is ample evidence from animal experiments that gastrointestinal motility including gastric emptying is altered by intestinal inflammation (43), pathomechanisms causing delayed gastric emptying in inflammatory diseases of the human distal gastrointestinal tract have not been investigated, so far. Specifically in CD, duodenal obstruction might impede gastric emptying; however, duodenal obstruction is a rare condition, none of our patients had evidence of upper gastrointestinal obstruction, and delayed gastric emptying has been demonstrated in patients with nonobstructive CD before (2). Thus, also in CD, regulatory disturbances more likely explain gastric motor disorders.

There is increasing evidence that patients with IBD have altered autonomic and enteric neural functions (10, 16, 40, 45, 54). Such neural disturbances have not been addressed by our study protocol but may contribute to gastric emptying disturbances in IBD patients (29) and deserve further investigation.

Experimentally induced acute hyperglycemia and even increases in blood glucose within the physiological range inhibit gastric emptying, both in diabetics and healthy subjects (15, 53). Because steroid-treated IBD patients may have elevated blood glucose, we assumed that this might explain delayed gastric emptying. Indeed, our patients had significantly increased postprandial blood glucose in correlation with steroid dose. However, blood glucose did not differ between CD and UC and was not associated with gastric emptying in either disease.

Patients with diverticulitis had significantly increased postprandial plasma glucose compared with healthy volunteers and IBD patients. Although diverticulitis patients were significantly older than the other groups, we intentionally excluded patients with known disturbances of blood glucose control or corticosteroid medication. Moreover, none still received parenteral nutrition that might have explained high blood glucose. Because there was a very close direct correlation between late postprandial plasma glucose and gastric emptying, it is intriguing to hypothesize that increased blood glucose may be a major determinant of delayed gastric emptying in diverticulitis.

Together with cholinergic mechanisms, CCK is a pivotal regulator for the integration of upper gastrointestinal secretory and motor functions. It is released in response to duodenal
nutrient exposure and stimulates pancreaticobiliary secretions (42) while inhibiting gastric emptying (4) (“duodenal brake”). Other candidates include GLP-1 and PYY, which are mainly released from the distal ileum and colon and inhibit upper gastrointestinal functions including gastric emptying (“ileal brake”) (26, 27, 31, 32, 48, 55). Thus we hypothesized that delayed gastric emptying might be a consequence of disturbed release of CCK and/or PYY and/or GLP-1.

According to our data, postprandial plasma concentrations of these hormonal mediators vary markedly, also within each group of patients. This is probably explained by patient heterogeneity. Still, we observed significant alterations of hormone release in patients with CD, UC, or DIV that appeared to be associated with the type of disease.

In CD, postprandial CCK plasma concentrations were increased markedly and persistently throughout the postprandial period. In some patients, excessive CCK release occurred postprandially with plasma concentrations exceeding 25 pmol/l, which, in humans, only have been observed in response to CCK antagonists, so far (23, 39). By contrast, healthy subjects, patients with UC, and patients with diverticulitis showed the expected moderate and transient increase in CCK plasma concentrations postprandially.

Only few previous studies have measured CCK release in IBD patients, so far, generally to clarify the mechanism for the high prevalence of gallstones (33, 57, 60). The one study that included healthy subjects (60) reported increased fasting but normal postprandial CCK plasma levels in patients with inactive CD. By contrast, our findings suggest that excessive postprandial release of CCK might contribute to delayed gastric emptying in CD patients with no or moderate disease activity because there was a weak, albeit significant, direct correlation between mean postprandial CCK concentrations and duration of gastric emptying.

Apart from regulatory effects on the upper gastrointestinal tract, CCK also reduces appetite and food intake via central effects; supraphysiological CCK levels induce nausea (5, 6, 14, 21). Thus excessive CCK release might explain why some patients with CD have severe symptoms of gastroparesis that are refractory to tube feeding (30). Studies with selective CCK antagonists are needed to further elucidate whether there is a causal relationship between increased CCK release and delayed gastric emptying in CD patients.

Fig. 5. Association between extension of disease and CCK plasma levels or gastric emptying, respectively, in CD patients. Patients with exclusively ileal disease (n = 4) had significantly higher maximal postprandial CCK plasma levels and a significantly longer T½ of gastric emptying compared with patients with affection of the colon with or without additional affection of more proximal gastrointestinal sites (n = 8). Data show means ± SD. GI, gastrointestinal.
Moreover, it remains to be clarified why CD patients as a group show markedly increased CCK release and why individual patients have excessively high CCK levels. Mucosal inflammation may contribute to these disturbances, and elevated postprandial CCK concentrations have been observed in patients with upper but not lower gut infections (PhD thesis Fiona Leslie, University of Manchester, UK, 2004) and in pigs and rats infected with nematodes (17, 62). In rats CCK appears to be implicated in the defense against intestinal bacteria (61) and has been shown to significantly reduce the lipopolysaccharide-induced increase in serum TNF-α, IL-1β, and IL 6 with protective effects on the lung (36). This constitutes a hypothetical connection between inflammatory mechanisms and increased CCK levels in IBD.

We observed slightly higher postprandial PYY plasma levels in UC and CD than in controls, but differences failed to reach statistical significance. Only single IBD patients had remarkably high PYY plasma concentrations (>100 pmol/l). Thus our data are generally in line with previous findings showing moderately increased PYY plasma concentrations in IBD (1, 28). In contrast to patients with IBD those with acute diverticulitis had significantly increased plasma PYY throughout the postprandial period, but there was no association with gastric emptying velocity.

Generally, there is little information on GLP-1 release in IBD patients, so far (7, 41, 49). In particular, to our knowledge, GLP-1 responses to a normal, mixed meal in noncolectomized patients with UC and in patients with CD have not been studied before. Our findings show significantly increased postprandial GLP-1 plasma concentrations in UC with no obvious association with gastric emptying parameters. In CD, elevated late postprandial GLP-1 levels are associated with, and therefore might contribute to, delayed gastric emptying. However, the increase in GLP-1 levels in a subset of CD patients only reached about twice the upper level of normal, whereas CCK levels exceeded more than five times the upper level of normal in single patients (Fig. 4).

In contrast to IBD, GLP-1 was strongly decreased in diverticulitis. It is intriguing to hypothesize that low GLP-1 levels might cause postprandial hyperglycemia, which in turn delays gastric emptying in diverticulitis. Systematic studies are needed to test this hypothesis.

In conclusion, this exploratory study suggests that patients with distal small bowel and colonic inflammation may have delayed gastric emptying and that this applies to both acute and chronic inflammatory disorders. Gastric emptying disturbances appear to be most pronounced in CD, but a subset of patients with diverticulitis or UC also have delayed gastric emptying. Systematic studies are needed to test this hypothesis.

GASTRIC EMPTYING IN DISTAL BOWEL INFLAMMATION

REFERENCES


