EVALUATION OF GASTRIC INFLAMMATORY PARAMETERS CAUSED BY PYLORIC RING FAILURE

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ABSTRACT

Introduction*: We aimed to compare the inflammatory parameters of patients with have failure of pyloric ring with those of that have intact pyloric ring.*

Material and methods*: Patients who underwent upper gastrointestinal endoscopy between May and September 2017 included in this study. The data of the study were collected prospectively and analysed retrospectively.*

Results*: A total of 205 patients were included in this study. 69 (33.7 %) male and 136 (66.3%) female patients, the mean age was 40.1 ± 11.38 years. Endoscopically, failure of pyloric ring was detected in 86 patients and intact pyloric ring in 119 patients. The histopathological examination of antrum; chronic gastritis in 91 patients (44.4 %), active chronic gastritis in 89 patients (44.3%) and normal findings were found in 23 patients (11.2%). The histopathological examination of corpus; chronic gastritis in 105 patients (51.2%), active chronic gastritis in 25 patients (12.2%) and normal findings were found in 73 patients (35.6%). Comparing the patients that have intact and pyloric ring failure, the inflammation and activation scores and Helicobacter Pylori (H. Pylori) density were higher in pyloric ring failure group (p:0.001, p: 0,018, p: 0,006). It was seen that in patients with pyloric ring failure had a significant decrease in inflammatory activation and H. Pylori density toward from antrum to the corpus, and this was statistically significant (p: 0.001, p: 0.001, p: 0.001).*

Conclusion*: Because of the high inflammatory histopathologic parameters caused by pyloric ring failure, these patients should be followed closely.*

Keywords: *Intestinal metaplasia, Bile reflux, Failures of pyloric ring, Gastric imflammation, Helicobacter Pylori, Gastric cancer.*

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Introduction

Duodeno gastric reflux (DGR) is defined as duodenal content's reflux from the duodenum to stomach[(1)]. The effects of chronic biliary reflux have been studied either by experimental models or by evaluating mucosal injury after surgical procedures such as gastric resection, pyloroplasty or gastroenteric anastomosis. In mucosal damage caused by DGR, the number of inflammatory cells increases in the gastric mucosa, parietal cells decrease, and glandular morphology changes due to hyperplasia in mucous cells[(2)]. These events have been associated with gastric intestinal metaplasia, reflux esophagitis, barrett esophagus and even adenocancer development[(3-7)]. Even the bile acids are shown to have an antibacterial effect against H. Pylori, there are conflicting results in the literature[(8)].

Therefore, the demonstration of the pathological effects of chronic bile reflux due to pyloric ring failure in patients without gastric resection combined by or absence of H. Pylori is clinically important and there are few studies in the literature with this regard. In this study, we aimed to compare the histopathological inflammation parameters which means that lymphocytes and neutrophils infiltrate the mucosa in a characteristically manner in patients that intact and failure of pyloric ring in upper gastrointestinal endoscopy.

Material and methods

Patients who underwent upper gastrointestinal endoscopy between May and September 2017 included in this study. We retrospectively reviewed a prospective database of a tertiary referral center. The demographic, endoscopic, and histopathological find-

ings of the patients were compared. Endoscopically, status of pyloric ring (failure or intact) ,erythema, erosion, ulcer, metaplastic areas, presence of bile at antrum, corpus and cardiac regions of stomach were evaluated. Antrum and corpus biopsy specimens were buffered in 10% formalin solution and paraffin blocks were prepared and stained with Giemsa and Hematoxylin-Eosin[9]. H. Pylori density and gastric histopathological findings were evaluated by the pathologist who did not know the clinical background and endoscopic findings of the patient.

Patients whom previously underwent upper gastrointestinal or gastric surgery, patients with gastric cancer, patients who use non-steroid anti-inflammatory drug (NSAID), neuropathic diseases such as diabetes, inflammatory bowel disease (IBD), patients with collagen vascular disease and those who had H. Pylori eradication in the last year were excluded from this study.

In this study, we did not use quantitative parameters such as gastric pH monitoring, 24 hour gastric bile monitoring with devices such as bilitec 2000, hepatobiliary scintigraphy, amylase and bilirubin levels in gastric fluid. We planned to monitor and evaluate the patients according to the histopathological findings of intact and pyloric sphicter failure in the upper gastrointestinal endoscopy performed by the experienced endoscopist.

We describe the pyloric ring failure that the diameter of pyloric ring allows at least two endoscopes could pass comfortably, which does not contraction during the procedure and or causing DGR. The intact pyloric ring was described as which can be opened by direct contact with the tip of the endoscope and contracted during the procedure. Again, there is no exact description pyloric insufficiency or failure in literature.

All procedures were performed under propofol and midazolom sedation anesthesia, to exclude to the provocative bile reflux caused by vomiting. Written informed consent was obtained from all patients included in this study. The information was collected in accordance with the Declaration of Helsinki. The ethical committee approval was obtained for this study.

Statistical Analysis

Descriptive statistical methods such as mean, standard deviation, frequency, and percentage were used in the evaluation of the study data. The distribution of variables was checked by the Kolmogorov-Simirnov test. Independent sampling t - test, Mann - Whitney U test and Wilcoxon test were used in the analysis of quantitative data, chi - square test was used in the analysis of qualitative data. $P < 0.05$ was considered statistically significant.

Results

Upper gastrointestinal endoscopy was performed in 205 patients with dyspeptic complaints. 69 (33.7%) of the patients were male and 136 (66.3%) were female. The mean age of the patients was 40.1 ± 11.38. In the upper gastrointestinal endoscopy, pyloric ring failure in 86 patients and intact pyloric ring were detected in 119 patients. In the histopathological examination of antral biopsy, the chronic gastritis was found in 91 (44.4%), active chronic gastritis in 89 (44.3%) and normal findings in 23 (11.2%) patients. The chronic gastritis in 105 (51.2%), active chronic gastritis in 25 (12.2%) and normal findings in 73 (35.6%) were detected in the corpus biopsy.

There was no statistically significant difference between the groups in terms of age and gender (p:0.084, p:0.249). There was no statistically significant difference between the groups in terms of indigestion, belching, nausea-vomiting, gas or bloating feeling (p> 0,05).

When the histopathological parameters of the antrum were compared in patients that have intact and pyloric ring failure, there was a statistically significant difference between the H. Pylori density, inflammation and activation scores of the patients. But no significant difference was found in the atrophy and metaplasia scores (p: 0.006, p: 0.001, p:0.018) (Table 1).

Histopathological parameters	Failures in pylorus	Intact pylorus	p
H. Pylori density	2,17±0,88	1,83±0,78	0,006
Inflammation	2,79±0,68	2,35±0,83	0,001
Activation	1,79±0,84	1,50±0,65	0,018
Atrophy	1±0	1,09±0,92	0,391
Metaplasia	1,16±0,5	1,09±0,32	0,439

Table 1: Histopathological findings of antrum in intact and failure pyloric ring.

When the histopathological parameters of corpus were examined, only the inflammation scores were significantly different (p:0.002) (Table 2). When the data of 86 patients were examined who have pyloric ring failure, it was seen that the decrease in inflammation, activation and H. Pylori density scores were statistically significant toward from antrum to the corpus. (p: 0.001, p: 0.001, p:0.001) (Table 3).

Histopathological parameters	Failures in pylorus	Intact pylorus	p
H. Pylori density	1,33±0,56	1,23±0,46	0,181
Inflammation	1,97±0,77	1,72±0,69	0,002
Activation	1,16±0,43	1,14±0,39	0,637
Atrophy	1±0	1±0	1
Metaplasia	1±0	1±0	1

Table 2: Histopathological findings of corpus in intact and failure pyloric ring.

Histopathological parameters	Antrum	Corpus	p
H. Pylori density	2,17±0,88	1,33±0,56	<0,001
Inflammation	2,79±0,68	1,97±0,77	<0,001
Activation	1,79±0,84	1,16±0,43	<0,001

Table 3: Comparison of histopathological findings of antrum and corpus in pyloric ring failure.

Discussion

DGR is a risk factor for atrophy and intestinal metaplasia (IM) development[10]. Duodenal fluid increases inflammatory cells in the gastric mucosa and changes the glandular morphology by reducing parietal cells and mucous cell hyperplasia. These changes leading to esophagitis, gastritis, gastric and duodenal ulcers[2]. When gastric microenvironment resembles to duodenum, intestinal metaplasia develops in the gastric mucosa to reduce the mucosal damage caused by alkaline fluid.

In our study, the IM scores of patients with pyloric ring failure were high, but not statistically significant. We think that this is due to DGR caused by pyloric ring failure. DGR is physiological in the early morning and postprandial period[11]. However, excessive DGR causes gastritis, esophagitis, ulcers, gastric polyps, metaplasia, esophageal and gastric cancers[12]. In 30 to 40% of patients, DGR may be associated with reflux esophagitis or gastroesophageal reflux (GER). DGR is widespread in asymptomatic cases, as well as in patients with gastric and duodenal ulcer, pulmonary disease and whom underwent cholecystectomy[13]. Endoscopically, pyloric ring failure and duodenal gastric reflux, erythema and erosion, gastric atrophy, petechiae, gastric plea thickening, metaplasia, and history of gastric surgery may be associated with DGR diagnosis[14].

Gastric mucosal damage is caused by the release of vasoactive materials such as histamine due to mast cell degranulation, resulting in vascular congestion in lamina propria[15]. These findings can also be seen in other conditions such as H. pylori infection.

Patients which used proton pump inhibitors(PPI) have been shown to have higher gastric pH, which in turn increases mucosal damage and suggesting that DGR-induced inflammatory scores may be higher in patients that pyloric ring failure. In other words, gastric acid has a protective effect against DGR and GER. In particular, patients which used PPI, and who have pyloric ring failure should be followed closely and carefully for gastric cancer[16].

It has been shown that enzymes such as trypsin and PLA2 in biliary and pancreatic juice in DGR cause damage to gastric mucosa[17]. Bile reflux causes antral G-cell hyperplasia and hypergastrinemia and reduces somatostatin release[18,19]. Decreased somatostatin levels increases the hypergastrinemia and hypergatrinemia further increases the bile reflux[20]. Cholecystokinin-2 (CCK-2) is a gastrin-specific receptor and is expressed in gastric pariatel cells and ECL cells[21]. CCK-2 receptors are exposed in normal esophagus, reflux esophagitis, barrette esophagus and adenocarcinoma[22]. It is known that H. Pylori is caused by precancerous lesions. Therefore, it was seen that the intensity of H. Pylori was increased in patients with have pyloric ring failure and it was accompanied synergistically with precancerous lesions such as atrophic gastritis and intestinal metaplasia. Therefore, hypergastrinemia due to chronic biliary reflux, gastric epithelial hyperplasia and gastric gland expansions are caused by the same mechanism. Previously, only endoscopic examination of DGR was reported to be intuitive and subjective, and endoscopic findings would not be sufficient[23]. In our study, we found that histopathological scores were higher in patients which have pyloric ring failure by endoscopically.

We consider that, the status of the pyloric ring (failures or intact) can be evaluated during the procedure due to the simplicity of the method and that the endoscopic findings alone are adequate for predicting risky patients.

Biliary reflux can not be diagnosed in the upper gastrointestinal endoscopy with the presence of bile in the stomach. Fuchs et al. described DGR in gastric fluid with high pH, demonstrating bilirubin and pancreatic enzymes[24]. 99mTc-EHIDA (99m Tc-ethyl hepatic iminodiacetic acid) scintigraphy showed 78.7% of cases diagnosed with DGR[23] Bile acids have a surfactant effect and this effect is necessary for lipid

absorption. This effect is due to hydrophilic-hydrophobic balance. If the surfactant effect is too strong, the effect is cytotoxic. The hydrophilic and hydrophobic balance shifts hydrophobic to increase the toxic effect on the epithelium[25,26]. The diagnosis of bile reflux should be made carefully, excluding H. Pylori infection, NSAID with alcohol use, and other factors that cause mucosal inflammation.

After distal gastrectomy, it is thought that bilroth 2 increases the risk of remnant gastric cancer, according to bilroth 1, and it is thought to be the effect of bile acids in duodenal fluid[27]. It was showed in an experimental study, that rats infected H. Pylori and underwent pyloroplasty, have positive correlation between metaplasia, dysplasia and cancer development. Neoplasia was observed in 40% of rats that underwent pylorplasty[28]. Metastasis is a multi-step process and epithelial cells need to be transformed into mesenchymal cells (Epitelial-mesenchymal transition-EMT). Loss of epithelial proteins such as E-cadherin and increased mesenchymal proteins such as N-cadherin and vimentin have been associated with advanced stage and poor prognosis in gastric cancer[29].

Normal gastric mucosa and gastric cancers express a high rate of bile acid receptor, G-protein-coupled receptor (GPBAR1), which is strongly associated with N-cadherin that EMT[30].

In the absence of biliary fluid in the stomach, DGR can not be diagnosed or 24 hour pH monitorizations or scintigraphic gastric aspiration and radiological studies may be required. We also think that it is important to specify the status of the pyloric ring and mucosal changes such as atrophy, metaplasia, as well as biliary fluid in stomach for the diagnosis of DGR. Because histopathologic findings of DGR may be seen in other situations such as H. Pylori infection, NSAID use. It is important to use simple, reliable and easily reproducible methods for the diagnosis of DGR.

As we have shown in our study, the presence of pyloric ring failures and the histopathological changes such as inflammation and activation can be combined to diagnose of DGR even if the absence of biliary fluid in the stomach.

The study suffered from several limitations. Due to the gastric fluid amylase and bilirubin levels were not measured, the level of damage due to the pancreatic or bile secretions were not shown.

Since it is a risk factor for carcinogenesis, multiple biopsies should be taken from patients with pyloric failure in upper gastrointestinal endoscopy and should be follow-up close for the carcinogenesis cascade. We recommend the addition of pyloric ring failure to DGR-associated risk factors which has described in the literature.

Conclusion

DGR is a risk factor for atrophy and IM development. Because of higher histopathological inflammation scores caused by DGR which patients that have pyloric ring failure, it is important that patients have close follow-up with multiple biopsies by yearly.

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