

学位論文の要旨

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学位論文名 Relationship Between Esophageal Cardiac Glands and Gastroesophageal Reflux Disease

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論文内容の要旨

INTRODUCTION

Gastroesophageal reflux disease (GERD) is characterized by the presence of esophageal mucosal injury or reflux symptoms caused by abnormal reflux of acidic gastric contents into the esophagus. The secretion of mucous from esophageal glands is important for protecting the mucosal surface from the pepsin and protease contained in gastric juices. There are two types of secretory glands in the esophagus: superficial glands located in the proper mucosal layer and deep mucous glands located in the submucosa. Superficial mucosal glands are found in the upper esophagus and near the junction with the stomach. Those located in the distal esophagus resemble the cardiac glands of the cardia, so these glands are called esophageal cardiac glands. The role of esophageal cardiac glands has not been fully determined. This study was performed to clarify the protective role of esophageal cardiac glands against the development of GERD.

MATERIALS AND METHODS

The subjects included 2,656 Japanese individuals who visited the Health Center of Shimane Environment and Health Public Corporation for a detailed medical checkup between April 2011 and March 2012. Patients who had taken medications such as proton pump inhibitors,

H2 receptor antagonists or prokinetic drugs within the preceding three months were excluded. Individuals with a history of gastric surgery, those who had received eradication therapy for *Helicobacter pylori* infection were not included in this study.

GERD symptoms were assessed using the Japanese version of the Carlsson-Dent self-administered questionnaire (QUEST). We defined subjects with a QUEST score of 6 or more as being positive for reflux symptoms. The body mass index (BMI) and current smoking and drinking (equivalent to over 50 mL of alcohol per day) habits were also noted. All subjects underwent an upper gastrointestinal endoscopy examination. The endoscopic findings of reflux esophagitis were evaluated using the Los Angeles (LA) classification, and individuals with a grade of A, B, C or D were diagnosed as being positive for reflux esophagitis. The size of the diaphragmatic hiatus was also assessed and categorized into three groups (<1.0, 1.0~2.0, >2 cm). The degree of gastric mucosal atrophy was evaluated endoscopically using the classification of Kimura and Takemoto, according to which gastric mucosal atrophy was classified into six groups (C1, C2, C3, O1, O2; O3). In this study, we defined C1-C2 as mild, C3-O1 as moderate and O2-O3 as severe gastric mucosal atrophy. The presence of esophageal cardiac glands was determined based on the detection of a visible yellowish elevated area on the distal esophagus, and the distribution of these lesions was assessed by dividing the findings into four grades (grade 0: absence of esophageal cardiac glands, grade 1: 1-5 spots indicating esophageal cardiac glands, grade 2: continuous transversely extending esophageal cardiac glands involving less than 50% of the esophageal circumference, grade 3: continuous transversely extending esophageal cardiac glands involving at least 50% of the esophageal circumference). The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

We prospectively enrolled 2,656 subjects (mean age: 51.8±9.2 years, men: 1,835) in this

study, and esophageal cardiac glands were observed in 355 cases (13.4%). Esophageal cardiac glands were more frequently observed in women (17.1% vs. 11.7%). Reflux esophagitis was significantly less frequent in the cases with esophageal cardiac glands than in those without and no cases of grade 2 or 3 esophageal cardiac glands involved reflux esophagitis. GERD symptoms showed a tendency to be less frequent in the subjects with esophageal cardiac glands. Multiple regression analysis showed that male gender, high BMI, large diaphragmatic hiatus and smoking were shown to be significant risk factors for the presence of reflux esophagitis, while the presence of esophageal cardiac glands and gastric mucosal atrophy were found to be independent factors related to its prevention. On the other hand, the presence of esophageal cardiac glands was not a significant preventive factor for the presence of GERD symptoms by multiple regression analysis. The esophageal cardiac glands were mainly located on the left-posterior side of the esophageal wall of the distal esophagus.

The results of this study demonstrated that esophageal cardiac glands play a protective role against esophageal mucosal injury in the distal esophagus. However, they do not inhibit the development of GERD symptoms. The acidic refluxate may stimulate the esophageal mucosa not covered with secreted mucous from esophageal cardiac glands and may induce reflux symptoms.

An interesting observation in this study is that the esophageal cardiac glands were found to be mainly located on the left-posterior side of the esophageal wall, which is opposite the main site of mucosal injury in patients with LA-classification A and B grade reflux esophagitis. The direction of esophageal mucosal injury in patients with reflux esophagitis may be influenced by the presence of esophageal cardiac glands, which have an acid-neutralizing function.

CONCLUSION

Esophageal cardiac glands may have a protective role against esophageal mucosal injury caused by acidic gastric contents.

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論文審査の結果の要旨

食道噴門腺は食道下端の粘膜固有層内に存在し、内視鏡検査時にしばしば食道粘膜表面に露出する黄白色の隆起として観察されるが、その役割は未だ不明である。そこで、本研究は食道噴門腺と胃食道逆流症 (Gastroesophageal Reflux Disease: GERD) の関係性を明らかにする目的で企画した。

対象は、本研究に同意が得られた上部消化管内視鏡を施行した2,656例 (全例人間ドック) で、年齢、性、BMI、喫煙・飲酒の有無、GERDの有無と症状、胃粘膜萎縮の程度、胃内反転観察法による食道裂孔開大の程度と食道噴門腺の存在位置および程度について検討し、結果は多重ロジスティック解析を行った。食道噴門腺は、全症例の13.4%に観察され、女性に有意に多かった。食道噴門腺の存在とGERD症状の有無については明らかな関連性を認めなかったが、食道噴門腺を有する例では有意に逆流性食道炎が少なかった (2.5% vs. 11.4%)。また、食道噴門腺の局在については、その主座は左後壁側であった。これは従来報告されている軽症逆流性食道炎の局在の主座である右前壁側の反対側であり、食道噴門腺の存在が軽症逆流性食道炎患者の食道粘膜傷害の方向性に影響している可能性が考えられた。

以上のことから、食道噴門腺が粘膜傷害発症に対して抑制的に働いていることが明らかとなった。今後、食道噴門腺の存在と食道下端の酸の停滞の周在性についての検討など、軽症逆流性食道炎の粘膜傷害発症のメカニズムとの関連については、さらなる検討が必要である。