学 位 論 文 の 要 旨

氏名　　高橋　芳子

学　位　論　文　名　　Impact of the Composition of Gastric Reflux Bile Acids on Barrett's Esophagus

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著　　者　　名　　Yoshiko Takahashi, Yuji Amano, Takafumi Yuki, Yuko Mishima, Yuji Tamagawa, Goichi Uno, Norihisa Ishimura, Shuichi Sato, Shunji Ishihara, Yoshikazu Kinoshita

論 文 内 容 の 要 旨

INTRODUCTION

It is well known that not only acid reflux but also bile one into the esophagus plays an important role in the pathogenesis of erosive esophagitis and Barrett's esophagus. In particular, patients with Barrett's esophagus have been proven to have a high incidence of bile reflux. Therefore, the pathogenesis of Barrett's esophagus is suggested to be related not only to acid reflux but also to bile reflux. In animal models, reflux of duodenal contents was repeatedly shown to play an important role in the development of Barrett's esophagus and Barrett's carcinogenesis. However, the various effects of bile acids on the esophageal mucosa have not been fully investigated in humans. To evaluate the influence of bile acid composition of gastric juice on Barrett's esophagus, a prospective study was designed in human model.

MATERIALS AND METHODS

Consecutive patients (n = 50) with endoscopically identified Barrett's esophagus of length over 1 cm who were undergoing esophago-gastro-duodenoscopy (EGD) and whose specialized columnar epithelium (SCE) was histologically confirmed were enrolled in this study. As a control group, 100 consecutive patients without Barrett's esophagus who needed EGD for an annual medical check-up according to the local government anti-gastric cancer program were

studied. Patients were interviewed to identify possible long-term administration of proton pump inhibitors (PPIs) for over 12 months prior to the endoscopic examination.

Endoscopic study

Barrett's esophagus was diagnosed on endoscopy according to C&M criteria. Erosive esophagitis was diagnosed when esophageal mucosal breaks of grade A, B, C or D (Los Angeles classification) were found. The presence or absence of hiatal hernia and gastric mucosal atrophy was investigated endoscopically. Biopsy samples were taken from the esophageal squamous mucosa 1 cm above the squamo-columnar junction for all enrolled patients. In the 50 patients with Barrett's esophagus, biopsy samples were taken from the Barrett's mucosa approximately 1 cm below the squamo-columnar junction, in addition to the biopsy from the esophageal squamous mucosa. Gastric juice was endoscopically collected using an aspiration kit. To perform a sampling without any contamination, endoscopic premedication with dimethicone or a mucolytic agent was avoided.

Determination of bile acids in gastric juice

Gastric juice containing reflux bile obtained from the endoscopic procedure was immediately refrigerated. The concentration of bile acids in the gastric juice was measured with high performance liquid chromatography (HPLC) by SRL, Inc., a company providing laboratory testing services (Tokyo, Japan). In the present study, 6 bile acids were analyzed: lithocholic acid (LCA), glycolithocholic acid (GLCA), taurolithocholic acid (TLCA), glycoursodeoxycholic acid (GUDCA), tauroursodeoxycholic acid (TUDCA) and ursodeoxycholic aid (UDCA). The bile acid ratio (the ratio of hydrophobic bile acids with cytotoxic action to hydrophilic bile acids with cytoprotective action) was calculated as (LCA+GLCA+TLCA) / (UDCA+GUDCA+TUDCA) in all enrolled patients, and was named the bile hydrophobicity ratio (BHR) in this study.

Histopathology

Cyclooxygenase-2 (COX-2), proliferating cell nuclear antigen (PCNA) and bone morphogenetic protein (BMP)-4 protein expression were histochemically investigated in each biopsy specimen. COX-2 expression and the subsequent accelerated cellular proliferation were reported to be important factors for carcinogenesis of Barrett's esophagus, and their evaluation was useful for determination of the malignant potential. BMP-4, a member of the transforming growth factor β family, is abundantly and uniquely expressed in Barrett's esophagus, and is known as an early expression marker in the development of Barrett's esophagus.

RESULTS AND DISCUSSION

The presence of erosive esophagitis showed a positive correlation with a higher BHR. Age, gender, and PPI administration did not show any correlation with the BHR. BHRs were 0.26 ± 0.05 (mean ± SE) and 0.08 ± 0.02 in patients with and without Barrett's esophagus, respectively. A statistically higher mean BHR was found in patients with Barrett's esophagus. As a predictor for the presence of Barrett's esophagus, the highest odds ratio was found in the BHR, indicating that a BHR increase of 0.1 was associated with a 5.74-fold risk of the development of Barrett's esophagus. Other positive predictors were age, hiatal hernia, and the PCNA index of esophageal squamous epithelial cells. Thus, the ratio of hydrophobic to hydrophilic bile acids was proven to be correlated with the presence of Barrett's esophagus.

The incidence of COX-2 protein expression with over 25% staining of Barrett's epithelial cells was 64% in patients with Barrett's esophagus, and Spearman's rank correlation tests showed a correlation between the BHR and COX-2 protein expression in patients with Barrett's esophagus ($r = 0.56$, $p < 0.001$). However, in the esophageal squamous epithelium, a correlation was not found between the BHR and COX-2 protein expression ($r = 0.03$, $p = 0.667$). The BHR also showed a correlation with the PCNA index of Barrett's epithelial cells in patients with Barrett's esophagus ($r = 0.44$, $p < 0.001$) and that of esophageal squamous cells in all enrolled patients ($r = 0.25$, $p = 0.001$). The incidence of BMP-4 protein expression with over 25% staining of esophageal squamous cells was 66.6% and 31.6% in patients with and without erosive esophagitis, respectively ($p = 0.023$), although it was 38.0% and 31.0%, respectively, in patients with and without Barrett's esophagus. BMP-4 protein expression in the esophageal squamous epithelium correlated with the BHR ($r = 0.37$, $p < 0.001$). Thus, bile reflux may affect on Barrett esophagus through COX-2 and BMP-4 protein expression and subsequent cellular proliferation of Barrett's epithelial cells.

CONCLUSION

Patients with Barrett's esophagus had a higher BHR in the gastric juice than patients without Barrett's esophagus. Therefore, changes of the bile acids composition may play an important role for the pathogenesis of Barrett's esophagus.