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ORIGINAL ARTICLE

Fundic gland polyps accurately predict a low risk of future gastric carcinogenesis

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Summary
Objectives: Few reports have analyzed the clinical importance of sporadic fundic gland polyps (FGPs). The aim of this study was to investigate the relationship between sporadic FGPs and condition of the gastric mucosa stratified by serum pepsinogen levels and *Helicobacter pylori* antibody level.
Methods: Three hundred and seventy-five subjects undergoing gastrointestinal endoscopy were enrolled. Subjects on proton pump inhibitors were excluded. Pathologically proven FGPs, and other endoscopic findings (reflux esophagitis, gastric and duodenal ulcer) were examined and serum pepsinogen levels, *H. pylori* antibody concentration and gastric juice pH were measured simultaneously. Subjects with normal serum pepsinogen and negative *H. pylori* antibodies were defined as having ''low risk'' stomachs, suggesting low risk of gastric carcinogenesis.
Results: Of the 375 subjects, 44 showed FGPs. The prevalence of ''low risk'' stomach in subjects with and without FGPs was 98% and 48%, respectively. Multivariable logistic regression analysis indicated three variables as independent factors positively associated with ''low risk'' stomachs: FGPs (odds ratio [OR] 38.6), reflux esophagitis (OR 4.8), and age < 60 years (OR 1.89). Gastric juice pH, which is associated with mucosal atrophy grade and low pH indicates less mucosal atrophy, was significantly lower in subjects with (1.64 ± 0.64) than without FGPs in ''low risk'' (1.94 ± 1.12) and ''high risk'' stomachs (3.99 ± 2.31).

Abbreviations: FGPs, Fundic gland polyps; *H. pylori*, *Helicobacter pylori*.

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Conclusions: Sporadic FGPs tend to be related to the least atrophic mucosa among non-gastric atrophy subjects without *H. pylori* infection, and can be used as predictors of a low risk of gastric carcinogenesis.

Introduction

Fundic gland polyps (FGPs) are the most prevalent type of gastric polyps, followed by adenomatous polyps, and are regarded as benign, non-neoplastic lesions [1,2]. FGPs are of three types: sporadic FGPs, familial adenomatous polyposis syndrome-associated FGPs, and pharmacologically induced FGPs. Sporadic FGPs have been reported to occur most often in females and to develop exclusively in patients without *Helicobacter pylori* infection [1,3—5], and have also been reported to be associated with a mutation of the beta-catenin gene [6]. FGPs also occur in up to 53% to 84% of patients with familial adenomatous polyposis; however, these FGPs are extremely rare [7]. The association between FGPs and acid suppression therapy has been supported by several investigators, and several prospective studies have reported the development of FGPs during long-term use of proton pump inhibitor therapy [8,9].

Recently, Genta et al. [10] reported for the first time a significant inverse correlation between FGPs and gastric neoplasia in a large study of over 100,000 patients. However, the precise association between sporadic FGPs and the condition of the gastric mucosa was not elucidated in the report by Genta, because users of proton pump inhibitors were not excluded.

Atrophic gastritis can be diagnosed non-endoscopically by assaying serum levels of pepsinogen. Reduced levels of serum pepsinogen-I and the ratio of serum pepsinogen-I/II are reliable markers for atrophic gastritis, a high risk precursor of gastric cancer [11—15]. The recent combined analysis of *H. pylori* seropositivity and mucosal atrophy determined by the serum pepsinogen method allows better stratification of the risk for development of gastric cancer than pepsinogen measurement alone [13—17]. This screening method is also effective for detecting the population exhibiting a low risk of stomach carcinogenesis, i.e., without gastric mucosal atrophy and inflammation [13—16].

Ohata [17] reported that no cancer developed in subjects with negative *H. pylori* infection and normal pepsinogen status during a follow-up of 4655 patients for a period of 7.7 years, and several other investigators [13,14,16] also reported an extremely low incidence of gastric cancer in subjects without gastric mucosal atrophy and inflammation. However, it is important to evaluate atrophy using only objective endoscopic findings during routine endoscopy. Although the sensitivity of endoscopic diagnosis of atrophy is relatively low [18], simple and objective endoscopic discrimination of atrophic mucosa is an important way of identifying subjects with low risk stomachs in clinical practice in whom frequent endoscopy is unnecessary and should be avoided. We hypothesized that FGPs could serve as useful markers for effective evaluation of the grade of mucosal atrophy.

In the present study, we examined the relationship between FGPs and the gastric mucosal condition, stratified by pepsinogen and *H. pylori* immunoglobulin G (IgG) antibody status, in a population strictly excluding subjects using histamine-2 receptor antagonists or proton pump inhibitors. Our aim was to evaluate the background gastric mucosal condition in subjects with sporadic FGPs and to determine whether sporadic FGPs can be a predictor of low risk stomachs, i.e., those without mucosal atrophy and inflammation.

Methods

Subjects

Between 2007 and 2012, we prospectively enrolled 375 subjects aged 21 to 86 years who attended Tokyo Dental College Ichikawa General Hospital outpatient clinic for routine upper gastrointestinal endoscopy. Gastrointestinal endoscopy was performed using electrical panendoscopes (types XQ260, Olympus, Tokyo, Japan). All endoscopies were performed by a single experienced gastroenterologist (HK). Exclusion criteria were as described previously [15,19]. Patients treated with proton pump inhibitors and histamine-2 blockers within 6 months of study enrollment and patients who had received *H. pylori* eradication therapy were strictly excluded, since proton pump inhibitors and eradication therapy for *H. pylori* significantly affect serum pepsinogen levels, and thus gastric mucosal atrophy cannot be accurately evaluated by pepsinogen measurement [20].

Esophageal mucosal breaks with esophagitis were graded according to the Los Angeles Classification of Esophagitis [21]. Reflux esophagitis was diagnosed when endoscopic findings of reflux esophagitis were grade A (no longer than 5 mm mucosal breaks) or above. Gastric or duodenal ulcer was diagnosed when at least one ulcer or ulcer scar having a diameter of > 5 mm was verified [22].

This study was approved by the Tokyo Dental College Ichikawa General Hospital Ethics Committee and was conducted according to the principles of the Second Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

Assays for antibodies against *H. pylori* and for serum pepsinogen-I and pepsinogen-II

Measurement of serum pepsinogen-I, pepsinogen-II and *H. pylori* IgG antibodies was contracted out to Mitsubishi Chemical Medience Co., Ltd. (Tokyo, Japan) as described previously [15,19]. Subjects with antibody concentrations < 10 U/mL were categorized as infection-negative; those with a concentration ≥ 10 U/mL were designated as