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Diabetes mellitus increases the risk of early gastric cancer development

Akira Sekikawa [a,1,*], Hirokazu Fukui [b,1], Takanori Maruo [a], Takehiko Tsumura [a], Yoshihiro Okabe [a], Yukio Osaki [a]

[a] Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Osaka, Japan
[b] Division of Upper Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

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Abstract ***Background:*** The significance of diabetes mellitus (DM) in gastric carcinogenesis still remains unclear. We investigated whether DM would be a risk factor for the development of early gastric cancer.
Methods: Factors related to the presence of gastric cancer were examined in patients undergoing medical health checkups. We then investigated whether DM was related to the development of early gastric cancer during an endoscopic follow-up study.
Results: Gastric cancer was detected in 14 (1.0%) of 1463 patients at the first endoscopic examination and was significantly associated with the severity of gastric atrophy and the presence of DM. During the follow-up period (range 36–108 months; mean 70.0 months), early gastric cancer was newly detected in 26 (1.8%) of the 1449 patients in whom gastric cancer had not been detected at the first examination. Gastric cancer was detected in 17 (1.3%) of 1301 patients without DM, and in 9 (6.1%) of 148 patients with DM ($P < 0.0001$). Multivariate analyses demonstrated that open-type gastric atrophy and DM were independently related to the development of early gastric cancer ($P < 0.0001$ and $P = 0.020$, respectively). Gastric cancer was identified in 14 (5.1%) of 274 patients who had open-type atrophic gastritis without DM, whereas it was identified in 8 (16.0%) of 50 patients who had both open-type atrophic gastritis and DM ($P = 0.0042$).
Conclusion: DM increases the risk of early gastric cancer development.

* *Corresponding author:* Address: Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, 5-30, Fudegasaki, Tennoji-ku, Osaka 543-8555, Japan. Tel.: +81 6 6774 5111; fax: +81 6 6774 5131.
E-mail address: sekky@osaka-med.jrc.or.jp (A. Sekikawa).
[1] A. Sekikawa and H. Fukui contributed equally to this work.

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1. Introduction

Gastric cancer is one of the leading causes of cancer-related death worldwide [1,2]. Since the survival of patients with advanced gastric cancer is poor [3,4], detection and resection of the lesion at an earlier stage improve the chances of survival. In this context, an effective approach for surveillance of early gastric cancer is needed. Recently, numerous studies have shown that *Helicobacter pylori* infection is a definite risk factor for the development of gastric cancer, and gastric atrophy induced by *H. pylori* infection is widely accepted as a feature significantly related to the possible presence of gastric cancer [5–8]. Because of the high prevalence of *H. pylori* infection in the Asian adult population, many individuals present with gastric atrophy. However, only a small proportion of them develop gastric cancer, suggesting that *H. pylori* alone is unlikely to be responsible for gastric cancer. Accordingly, in addition to gastric atrophy, it is necessary to find a cofactor related to the development of gastric cancer.

Diabetes mellitus (DM) is a common and major disease worldwide. Increasing evidence indicates that patients with DM have a higher risk of not only cardiovascular disease, but also cancer in various organs [9–12]. Recently, several investigators have found a possible association between DM and cancer in the liver, uterus and colon [13–15]. However, few studies have focused on the relationship between DM and the development of gastric cancer. In the present study, we examined factors related to the presence of gastric cancer in patients undergoing medical health checkups and found that DM was associated with the presence of gastric cancer. Then, in an endoscopic follow-up examination, we investigated whether DM would be a risk factor for the development of early gastric cancer.

2. Patients and methods

2.1. Patients and procedures

The present study was based on historical cohort analysis of patients who underwent medical health checkups, including endoscopic examination of the upper gastrointestinal tract, between 2004 and 2013 at Osaka Red Cross Hospital. First, we examined the presence of gastric cancer in a total of 1463 patients and investigated the factors related to the presence of gastric cancer. Second, we investigated whether the presence of DM increased the incidence of gastric cancer development in a total of 1449 patients who did not have a gastric cancer lesion at the initial endoscopic examination. For inclusion in this endoscopic follow-up study, patients had to have (i) undergone follow-up endoscopic examination of the upper gastrointestinal tract, (ii) been followed up for longer than 3 years and (iii) had neither prior gastrectomy nor gastric cancer. The following factors were retrospectively examined for all patients: age, sex, severity of gastric atrophy and presence of DM and gastric cancer. The presence of DM was determined on the basis of medical history, the result of a 75-g oral glucose tolerance test and the fasting plasma glucose (FPG) level (>126 mg/dl) or haemoglobin A1c (HbA1c) level ($\geqslant$6.5%), as reported previously [16,17]. Each patient basically underwent annual endoscopic evaluation of the upper gastrointestinal tract and was examined for the presence or absence of gastric cancer. The diagnosis of gastric cancer was confirmed by histologic examination of tissue obtained by endoscopic mucosal or surgical resection. Controls matched with the patients for age/sex/gastric atrophy were also examined. This study was carried out with the approval of the Osaka Red Cross Hospital Ethics Committee, and informed consent was obtained from all patients.

2.2. Endoscopic procedure and evaluation of gastric atrophy

Endoscopic examination was performed using a pan-endoscope (GIF-Q260 or GIF-H260; Olympus Medical Systems, Tokyo, Japan) equipped with an electronic endoscopy system (EVIS LUCERA system; Olympus Medical Systems). Experienced endoscopists performed each examination, carefully observing the oesophagus, the entire stomach and the bulbar portion of the duodenum.

We classified the severity of gastric atrophy according to the criteria of Kimura and Takemoto, as reported previously [18,19]. Briefly, by identifying the location of the borderline between the fundic and pyloric gland regions, the stage of atrophy was divided into three types: open-type, closed-type and antral-type. If the borderline between the fundic and pyloric regions was located in the angular part of the lesser curvature, it was defined as the antral-type. If the borderline was located on the lesser curvature of the stomach, it was defined as the closed-type. If the entire aspect of the lesser curvature was pyloric in nature, and the border was shifted orally, it was defined as the open-type.

2.3. Statistical analysis

Statview 5.0J statistical software (Abacus Concepts Inc., Berkeley, CA, United States of America) was used for all analyses. Data for age were expressed as the mean $\pm$ SEM. Differences in these values between two groups were analysed using unpaired two-tailed t test or by Mann–Whitney U-test when the data were not parametric. Chi-squared analyses were performed to investigate the relationships between groups and the various clinical features, and Fisher's exact test was also used as necessary. Univariate and multivariate Cox