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Metformin use is associated with a decreased incidence of colorectal adenomas in diabetic patients with previous colorectal cancer

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ABSTRACT

Background: Metformin use has been associated with decreased cancer risk and mortality. However, the effects of metformin on the development of colorectal adenomas, the precursors of colorectal cancers, are not defined.

Aims: This study aimed to evaluate the potential effect of metformin on the incidence of colorectal adenomas in diabetic patients with previous colorectal cancer.

Methods: Among 488 consecutive diabetic patients who underwent colonoscopic surveillance after curative resection of colorectal cancer between 1998 and 2008, 240 patients were enrolled in this study and were compared in two groups: 114 patients taking metformin and 126 patients not taking metformin. Patient demographics, clinical characteristics, and colorectal adenoma incidence rate were analysed.

Results: After a median follow-up of 58 months, a total of 33 patients (28.9%) exhibited adenomatous colorectal polyps among the 114 patients who used metformin, compared with 58 (46.0%) patients with colorectal adenomas among the 126 patients who did not use metformin (odds ratio = 0.48, 95% confidence interval = 0.280–0.816, $P = 0.008$). After adjustment for clinically relevant factors, metformin use was found to be associated with a decreased incidence of colorectal adenomas (odds ratio = 0.27, 95% confidence interval = 0.100–0.758, $P = 0.012$) in diabetic patients with previous colorectal cancer. Metformin use in diabetic patients with previous colorectal cancer is associated with a lower risk of colorectal adenoma.

1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death, with a lifetime risk of 5% [1,2]. Most CRCs develop from adenomas; it takes 10–15 years for an adenomatous polyp to evolve into clinically invasive cancer [3]. Therefore, screening and prevention are important strategies to lower the burden of CRC. Chemoprevention is one of the primary preventive strategies and refers to long-term use of a variety of oral agents that can delay, prevent, or even reverse the development of adenomas in the colon. Substantial evidence has shown that NSAIDs and selective COX-2 inhibitors can reduce the incidence of CRC and colorectal adenomas [4–6]; however, reports have revealed an increased risk of gastrointestinal bleeding and serious cardiovascular events [7,8]. Therefore, novel drugs that are both safe and effective are needed for CRC prevention.

Metformin, a biguanide derivative, is an oral drug widely used as a first-line therapy for type 2 diabetes. Metformin decreases basal glucose output by inhibiting hepatic gluconeogenesis and peripheral glycogenolysis. The molecular mechanism of metformin involves liver kinase B1 (LKB1)-dependent activation of AMP-activated protein kinase (AMPK) [9]. Activated AMPK inhibits the mammalian target of the rapamycin (mTOR) pathway, which plays a key role in cell growth and proliferation. Therefore, AMPK activation by metformin may have a suppressive effect on tumourigenesis and cancer cell growth. Interestingly, several experimental studies in animals suggest that metformin use may decrease the risk of colorectal adenomas [10,11]. They have shown that metformin induces AMPK activation and inhibits tumour development and growth, including colon carcinogenesis. In addition, population studies have shown that patients with type 2 diabetes who are taking metformin have a lower risk of cancer compared with patients who do not take metformin [12]. Recently, we found that metformin use is associated with lower risk of mortality in CRC patients with diabetes [13].

Although there has been substantial evidence from *in vivo* and *in vitro* studies supporting the potential efficacy of metformin as a chemopreventive agent, there have been no clinical studies investigating the effect of metformin on the prevention of colorectal

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adenomas. We undertook a retrospective cohort study of patients with a history of CRC, a high-risk group for adenomas, to evaluate the effect of metformin on the occurrence of new colorectal adenomas in diabetic patients.

2. Methods

2.1. Patients

Between January 1998 and December 2008 we identified 488 consecutive diabetic patients who underwent colonoscopic surveillance after curative resection of CRC at Severance Hospital, Yonsei University College of Medicine in Seoul, Korea. We obtained the medication data from the chart review based on self-report and pharmacy records. Among them, 248 patients were excluded based on the following exclusion criteria: incomplete records (including medication records); stage 4 patients, history of familial polyposis syndrome; known inflammatory bowel disease; other invasive cancer; incomplete colonoscopy before colorectal resection or within 6 months after operation; and localized tumour recurrences at the anastomotic site. Finally, 240 patients were enrolled in this study and were divided into two groups: 114 patients with consistent metformin use before and after CRC diagnosis and 126 patients not taking metformin. Patient demographics, clinical characteristics, surveillance colonoscopic findings, and the colorectal adenoma incidence rate were analysed. The use of other diabetic medications (sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, insulin, and so on) and aspirin was also investigated.

Patient demographics and clinical characteristics including age at diagnosis, gender, follow-up duration, duration of diabetes, family history of colorectal malignancy, body mass index (BMI), smoking history, and drinking history were obtained from medical records. Laboratory findings included pretreatment carcinoembryonic antigen (CEA) levels, plasma glucose levels, and haemoglobin A1c levels, as well as information pertaining to the CRC diagnosis, including stage, location, histology, differentiation, and treatment modality. The date of diagnosis of CRC was the day of pathologic diagnosis. All patients were assessed by the 6th version of the AJCC staging system derived from a synthesis of clinical, pathological, and imaging information. Treatment modality was decided upon by extension and location of the tumour. All patients underwent curative intent surgical resection for stage I, II, or III CRCs.

The institutional review board of Severance Hospital, Yonsei University in Seoul, Korea approved this study.

2.2. Colonoscopic surveillance

All patients received a baseline colonoscopy before colorectal resection or within 6 months after colorectal resection. In cases of obstructing CRCs, additional colonoscopic examinations were carried out within 6 months after operation and these findings were included as part of the baseline colonoscopic findings. We excised all adenomas detected during preoperative and postoperative colonoscopies. Follow-up colonoscopy was done at least once and up to three times after operation during the follow-up period. The surveillance interval varied among patients from 6 months to 12 years. Given this diversity in the number of surveillance colonoscopies and surveillance intervals, we considered the total follow-up period and the timing of the first follow-up colonoscopy.

An advanced adenoma was defined as a tubular adenoma 10 mm or greater in diameter, an adenoma with villous or tubulovillous histology, or with high-grade dysplasia or carcinoma [14]. Patients were classified according to their most advanced histologic lesions. Patients with hyperplastic polyps and other benign mucosal lesions were not considered to have adenomas.

2.3. Statistical analysis

The primary endpoint of the current study was colorectal adenoma incidence rate. Secondary analyses compared the two groups with respect to the proportion of patients with advanced adenomas. The baseline demographics and characteristics of the patients were analysed with descriptive statistics. Continuous data were analysed using Student's *t*-test and categorical data were compared using Pearson's χ^2 test. Univariate logistic regression analysis was used for univariate analysis of the colorectal adenoma incidence rate. A multivariate logistic regression model was used to evaluate the colorectal adenoma incidence rate to adjust for various confounders. A Kaplan–Meier model was used to evaluate the cumulative probability of colorectal adenoma development; the survival curves of each group were compared by a log-rank test. A value of $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Patient demographics and clinical characteristics

Patient demographics and clinical characteristics are summarised in Table 1. The median patient age was 62 years (range, 33–82 years). Baseline characteristics including age at diagnosis, sex, follow-up duration, family history of CRC, BMI, smoking history, history of alcohol consumption, number of baseline colorectal adenoma, tumour stage, tumour location (colon or rectum), aspirin use, and pretreatment CEA level were not significantly different between the metformin group and the non-metformin group. Severity of diabetes as judged by haemoglobin A1c levels, pre-meal glucose levels, and duration of diabetes were not different between the two groups. We also evaluated the use of other diabetic medications because there is evidence that these medications, including insulin and thiazolidinediones, may affect the development of colorectal adenomas [15,16]. Insulin and thiazolidinedione use were not significantly different between the two groups. In addition, a comparison of the treatment modality for CRC and the operation method in the two groups showed no significant difference.

3.2. Colonoscopic surveillance

In our study group, 177 patients (73.8%), 54 patients (22.5%), and 9 patients (3.8%) underwent follow-up colonoscopy once, twice, and three times, respectively. The number of follow-up colonoscopies was not significantly different between the metformin group and the non-metformin group ($P = 0.069$). The interval to the first follow-up colonoscopy was not significantly different between the two groups (24.4 months *vs.* 24.5 months, $P = 0.979$) (Table 2).

3.3. Findings of follow-up colonoscopy

The number of polyps and colorectal adenoma positive rate were examined in each follow-up colonoscopy, and in the 1st follow-up colonoscopy, colorectal adenoma positive rate of the non-metformin group was higher than that of the metformin group (43.7% *vs.* 28.1%, $P = 0.015$) (Table 3). Although there was no statistical significance, the non-metformin group still showed higher colorectal adenoma positive rates in the 2nd and 3rd follow-up colonoscopies.

3.4. Metformin use and colorectal adenoma incidence rate

The median follow-up duration was 48 months (range, 19–170). In the entire cohort, 91 (37.9%) patients exhibited colorectal adenoma development and 2 (0.8%) patients showed metachronous