The effect of metformin on recurrence of colorectal adenoma in diabetic patients with previous colorectal adenoma

Min Seok Han

Department of Medicine

The Graduate School, Yonsei University

The effect of metformin on recurrence of colorectal adenoma in diabetic patients with previous colorectal adenoma

Directed by Professor Tae Il Kim

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Min Seok Han

December 2016

This certifies that the Master's Thesis of
Min Seok Han is approved.

Thesis Supervisor: Tae Il Kim

Thesis Committee Member#1: Bong Soo Cha

Thesis Committee Member#2: Joong Bae Ahn

The Graduate School
Yonsei University

December 2016

ACKNOWLEDGEMENTS

This page is exclusively designed to note my gratitude and respect for those who helped me to complete my thesis. I am deeply indebted to my supervisor Prof. Dr. Tae Il Kim for his kind help, guidance, support and encouragement throughout my study. Sincere gratitude goes out to my reviewers, Prof. Dr. Bong Soo Cha and Prof. Dr. Joong Bae Ahn who had the patience and fortitude to read my thesis and provided constructive criticism to help me defend it. Their guidance not only improved my dissertation but also will benefit my future works. I also sincerely thank my colleagues, Jung Hyun Jo, Eun Suk Jung for their supports.

Finally, this thesis would not have been possible without my family. This small thesis is devoted to God.

Min Seok Han

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

The effect of metformin on recurrence of colorectal adenoma in diabetic patients with previous colorectal adenoma

Min Seok Han

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Tae Il Kim)

Existing studies suggest that metformin lowers the risk and mortality of colorectal cancer. However, the effect of metformin on the suppression and prevention of colorectal adenomas is not clear. The aim of this study was to evaluate the effect of metformin on the recurrence of colorectal adenoma in diabetic patients with previous colorectal adenoma. Among 423 diabetic patients who underwent surveillance colonoscopy after resection of colorectal adenoma between 2005 and 2011, 257 patients were retrospectively reviewed. The patients were divided into two groups: one group comprising 106 patients who took metformin and another group comprising 151 patients who did not take metformin. The clinical characteristics, colorectal adenoma recurrence, and valuable factors for adenoma recurrence were analyzed. At surveillance colonoscopy after colonoscopic polypectomy for adenoma, 38 patients (35.8%) exhibited colorectal adenoma among 106 patients who took metformin, compared with 85 patients (56.3%) with colorectal adenoma among 151 patients who did not take metformin (odds ratio 0.434, 95% confidence interval

0.260-0.723, P = 0.001). Multivariate Cox analysis showed that metformin was associated with decreased recurrence of colorectal adenoma (hazard ratio 0.572, 95% confidence interval 0.385-0.852, P = 0.006) in diabetic patients with previous colorectal adenoma. The cumulative probability of colorectal adenoma recurrence was significantly lower in the metformin group than in the non-metformin group (P = 0.001). Metformin use in diabetic patients with previous colorectal adenoma is associated with a lower risk of colorectal adenoma recurrence.

Key words: Metformin, Colorectal adenoma, Recurrence, Diabetes mellitus

The effect of metformin on recurrence of colorectal adenoma in diabetic patients with previous colorectal adenoma

Min Seok Han

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Tae Il Kim)

I. INTRODUCTION

Colorectal cancer (CRC) is a common neoplasm worldwide and the third main cause of cancer related death.[1] Colorectal adenoma is a precursor of colorectal cancer according to the adenoma-carcinoma sequence.[2,3] Suppression and removal of colorectal adenoma is very important for preventing colorectal cancer.[4] Recent studies proved that non steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors have chemopreventive effects against colorectal adenoma and cancer.[5-7] However, they have increased risks of gastrointestinal bleeding and cardiovascular accidents.[8] Thus, they are not usually used for chemoprevention, except for limited use in patients with very high CRC risk. Therefore, new drugs that are safe and effective for the prevention of colorectal adenoma are needed.

Epidemiological studies have shown that the risk of several types of

cancer, including cancer of the pancreas, liver, breast, colorectum, urinary tract, and female reproductive organs, is increased in patients with diabetes.[9] The mortality of these cancers is also moderately increased in patients with diabetes. In addition, diabetes mellitus is an independent risk factor for colorectal cancer, and diabetic patients with colorectal cancer have worse outcomes than non-diabetic patients.[10] Moreover, hyperinsulinemia most likely increases the risk of cancer in patients with diabetes, as insulin is a growth factor with preeminent metabolic and mitogenic effects.

Recently, metformin, a biguanide derivative oral diabetic agent, was reported to have a tumor-suppressive effect. Concerning its use as an anti-diabetic medication, metformin suppresses gluconeogenesis in the liver and reduces insulin resistance in peripheral organs, and shows no glucose lowering effect in non-diabetic patients. Moreover, metformin has been widely used for a long time in the treatment of type 2 diabetes mellitus and is generally considered to be a safe and economic drug, which means optimal candidate for a chemopreventive drug. The main action mechanism of metformin is related to liver kinase B1-dependent activation of AMP-activated protein kinase (AMPK).[11] In addition, activated AMPK inhibits the mammalian target of the rapamycin pathway (mTOR), which plays a key role in cell growth and proliferation. Therefore, AMPK activation by metformin may have a suppressive effect on tumorigenesis and cancer cell growth.[12] Furthermore, preclinical studies identified the anti tumor effect of metformin, the inhibition of tumor growth and induction of apoptosis in animals, and cell line models of various cancers.[13]

There have been some reports about the effect of metformin on decreased

risk and mortality of colorectal cancer. In a meta-analysis of 14 cohort studies revealed that the risk of colorectal cancer was significantly lower among metformin users than among non-metformin users (pooled risk ratio [95% confidence interval] 0.79 [0.69-0.91], test for overall effect Z=-3.34, P < 0.001).[14] As for the mortality of colorectal cancer, a meta-analysis of 6 cohort studies, including our previous study, metformin users had a better overall survival (hazard ratio 0.56, 95% confidence interval 0.41-0.77) and a better CRC-specific survival (hazard ratio 0.66, 95% confidence interval 0.50-0.87) than non-metformin users.[15]

However, there have been few reports about the effect of metformin on the suppression and prevention of colorectal adenoma, which is the precancerous lesion of CRC.[16,17] In our previous study, we reported the effect of metformin on colorectal adenomas, showing that metformin was 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 CRC.[18] However, because the patients in our previous study had colorectal cancer, the colon area of surveillance colonoscopy was limited owing to previous surgery, and we needed to prove the effect of metformin in the extended general population. Thus, we decided to evaluate the effect of metformin on the recurrence of colorectal adenoma in diabetic patients with previous colorectal adenoma.

II. MATERIALS AND METHODS

1. Study design

A total of 423 patients with diabetes who underwent surveillance colonoscopy after resection of colorectal adenoma between January 2005 and December 2011 at Severance Hospital, Yonsei University College of Medicine in Seoul, Korea, were enrolled initially. Among them, 166 patients were excluded because of the the following reasons: previous bowel resection (153 patients), poor bowel preparation (8 patients), familial polyposis (3 patients), and short follow-up duration(2 patients). Finally, 257 patients were retrospectively reviewed and divided into two groups: 106 patients who took metformin and 151 patients who did not take metformin (Fig. 1). We defined metformin takers as patients who took metformin $\geq$6 months during the follow-up duration between screening colonoscopy and surveillance colonoscopy.

We reviewed the medical records on age; sex; body mass index; family history of colorectal cancer; smoking history; diabetes mellitus duration; medication history; laboratory findings including hemoglobin A1c(HbA1c), glucose, and cholesterol levels; characteristics of adenoma; and colonoscopic follow-up duration.

The end point of our study was the difference in the recurrence rate of colorectal adenoma after polypectomy between the metformin and non-metformin groups.

We obtained approval from the institutional review board of Severance Hospital, Yonsei University, Seoul, Korea.

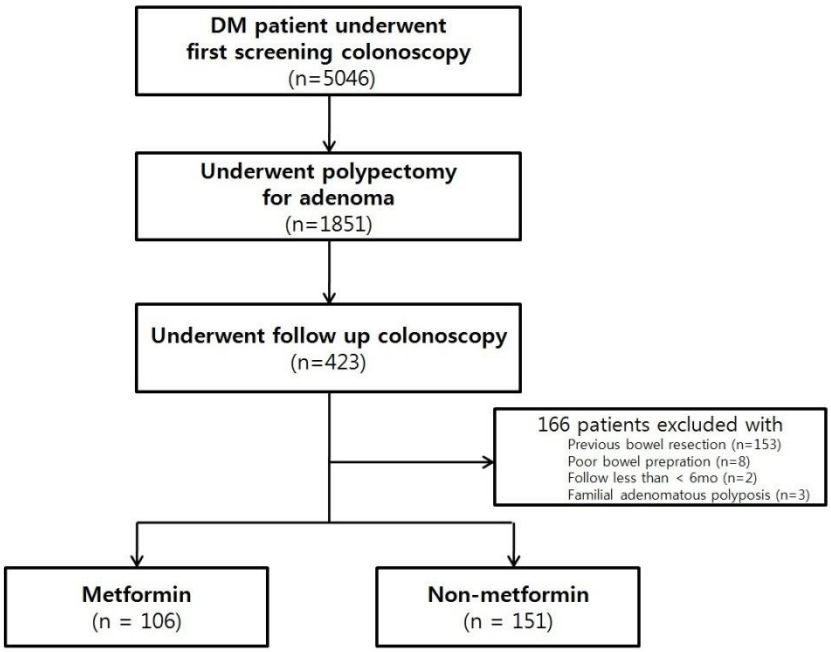

Figure 1. Overview of the patient selection process

2. Colonoscopic surveillance

The patients underwent screening colonoscopy and received polypectomy at the same time when a polyp was detected. Then, the patients underwent surveillance colonoscopy according to existing guidelines.[19] Hyperplastic polyps and other benign mucosal lesions were not considered as adenomas. We reviewed recurred adenoma at surveillance colonoscopy, including adenoma location, shape, size, and pathology. Advanced adenoma was defined as an adenoma that was ≥10mm in diameter and/or with high-grade pathology, including villous or tubulovillous component, high-grade dysplasia, and carcinoma.

3. Statistical analysis

We performed statistical analyses by using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Grouped values were reported as mean ± standard deviation of mean. To examine the differences between the metformin group and the non-metformin group, Student's t-test was used for continuous variables and the chi-square test was used for categorical variables.

We used both logistic regression and Cox regression models to evaluate the rate of colorectal adenoma recurrence and the valuable factors for adenoma recurrence. A multivariate analysis was performed for evaluation after adjusting for various confounders.

Kaplan–Meier and Cox proportional hazard models were used to evaluate the cumulative probability of colorectal adenoma development. In the

Kaplan–Meier model, the polyp recurrence curves of the two groups were compared by using a log-rank test. The Cox proportional hazard model was also used to evaluate the cumulative probability of colorectal adenoma development after adjusting for confounding factors. In each instance, 95% confidence intervals were also reported when available and $P < 0.05$ was required for statistical significance.

III. RESULTS

1. Patients demographics and clinical characteristics

The median follow-up duration was 27 months (range 10-65). The clinical characteristics are shown in Table 1. There was no significant difference between the metformin and non-metformin groups in clinicopathophysiologic characteristics including age, sex, family history of colorectal cancer, smoking history, diabetes mellitus duration, aspirin use, glucose level, cholesterol level, number of baseline adenomas, and colonoscopic follow-up duration. However, the metformin group showed higher body mass index and HbA1c level ($P = 0.004$ and $P = 0.032$, respectively), and less use of insulin ($P = 0.015$).

Table 1. Clinical characteristics of the metformin and non-metformin groups

	Metformin (n=106)	**Non-Metformin (n=151)**	***P*-value**
Age (years)	66.5±7.0	65.5±8.1	0.327
Sex			0.420
Male	76 (71.7%)	115 (76.2%)	
Female	30 (28.3%)	36 (23.8%)	
Body mass index (Kg/m^2)	25.4±3.5	24.2±3.0	0.004
Family History of CRC	6 (5.7%)	5 (3.3%)	0.369
Current smoker	28 (26.4%)	41 (27.2%)	0.439
DM duration (years)	8.2±4.4	9.3±4.2	0.290
Aspirin use	45 (42.5%)	67 (44.4%)	0.799
Insulin use	4 (3.8%)	19 (12.6%)	0.015
Thiazolidinedione use	11 (10.4%)	8 (5.3%)	0.149
Hba1c (%)	7.0±0.7	6.8±0.7	0.032
Glucose, AC (mg/dL)	110.3±18.3	114.0±20.7	0.388
Glucose, PC (mg/dL)	178.9±33.8	170.3±31.6	0.280
Total cholesterol (mg/dL)	179.4±23.9	176.8±27.9	0.440
Number of baseline adenomas	2.5±2.5	2.7±2.5	0.496
Time to first follow-up colonoscopy (days)	859±414	762±421	0.066

Values are presented as mean±standard deviation or n(%)

CRC, colorectal cancer; DM, diabetes mellitus, Hba1c, glycated hemoglobin; AC, ante cibum; PC, post cibos

2. Characteristics of adenomas found in surveillance colonoscopy

There was no significant difference in the characteristics of adenomas found in surveillance colonoscopy between the metformin and non-metformin groups except in the number of patients with recurrence of conventional adenoma (Table 2).

Table 2. Characteristics of adenomas found in surveillance colonoscopy in the metformin and non-metformin groups

	Metformin (n=106)	**Non-metformin (n=151)**	***P*-value**
Number of polyps	0.80±1.4	0.83±1.1	0.836
Size of largest polyp, mm	2.1±4.0	2.8±3.4	0.136
Location of adenomas			
Right side of colon	56 (63.6%)	63 (52.5%)	0.310
Left side of colon	23 (26.1%)	52 (43.3%)	0.076
Rectum	9 (10.2%)	5 (4.2%)	0.115
Dysplasia			
Non high-grade	83 (97.6%)	115 (97.5%)	0.984
High-grade	2 (2.4%)	3 (2.5%)	0.955
Type of adenomas			
Tubular adenoma	80 (94.1%)	116(98.3%)	0.929
Tubulovillous adenoma	2 (2.4%)	1 (0.8%)	0.370
Villous adenoma	3 (3.5%)	1 (0.8%)	0.386
Conventional adenoma, yes/no	37/69 (34.9%/65.1%)	85/66 (56.3%/43.7%)	<0.001
Serrated adenoma, yes/no	3/103 (2.8%/97.2%)	2/149 (1.3%/98.7%)	0.381
Number of conventional adenomas	85	118	0.897
Number of serrated adenomas	3	2	0.392

Values are presented as mean±standard deviation or n(%)

3. Comparison of the recurrence rate of colorectal adenoma between the metformin and non-metformin groups

Among a total of 257 patients, 123 (47.9%) exhibited recurrence of colorectal adenoma, and 2 (0.01%) exhibited colorectal cancer (Table 3). Among 106 patients who took metformin, 38 (35.8%) exhibited colorectal adenoma, whereas among 151 patients who did not take metformin, 85 (56.3%) exhibited colorectal adenoma (odds ratio 0.434, 95% confidence interval 0.260−0.723, P = 0.001). However, there was no significant difference in the recurrence of advanced adenoma and colorectal cancer.

In the subgroup analysis, the male patient group showed similar results (Table 4). Among 76 male patients who took metformin, 28(36.8%) exhibited colorectal adenoma, whereas among 115 male patients who did not take metformin, 70(60.9%) exhibited colorectal adenoma (odds ratio 0.375, 95% confidence interval 0.206−0.682, P = 0.001). However, in the female patient group, there was no significant difference in the recurrence of total adenoma (Table 5).

Table 3. Recurrence rate of colorectal adenoma and incidence of CRC in the metformin and non-metformin groups

	Metformin (n=106)	**Non-metformin (n=151)**	**OR**	**95% CI**	***P*-value**
Total adenoma	38 (35.8%)	85 (56.3%)	0.434	0.260-0.723	0.001
Advanced adenoma	20 (18.9%)	21 (13.9%)	1.440	0.737-2.814	0.287
CRC	1	1			1.000

CRC, colorectal cancer; OR, odds ratio; CI, confidence interval

Table 4. Recurrence rate of colorectal adenoma and incidence of CRC in the metformin and non-metformin groups (Male)

	Metformin (n=76)	**Non-metformin (n=115)**	**OR**	**95% CI**	***P*-value**
Total adenoma	28 (36.8%)	70 (60.9%)	0.375	0.206-0.682	0.001
Advanced adenoma	13 (17.1%)	15 (13.0%)	1.376	0.614-3.083	0.438
CRC	0	1			

CRC, colorectal cancer; OR, odds ratio; CI, confidence interval

Table 5. Recurrence rate of colorectal adenoma and incidence of CRC in the metformin and non-metformin groups (Female)

	Metformin (n=30)	**Non-metformin (n=36)**	**OR**	**95% CI**	***P*-value**
Total adenoma	10 (33.3%)	15 (41.7%)	0.700	0.256-1.917	0.488
Advanced adenoma	7 (23.3%)	6 (16.7%)	1.522	0.450-5.145	0.499
CRC	1	0			

CRC, colorectal cancer; OR, odds ratio; CI, confidence interval

4. Factors affecting the recurrence rate of colorectal adenoma

After adjustment for age, sex, body mass index, diabetes mellitus duration, aspirin use, insulin use, thiazolidinedione use, HbA1c, number of baseline adenomas, and time to first follow-up colonoscopy, multivariate logistic regression analysis showed that metformin use was associated with decreased recurrence of colorectal adenomas (odds ratio 0.433, 95% confidence interval 0.256−0.732, P = 0.002) in diabetic patients with previous colorectal adenoma. Furthermore, the number of baseline adenomas was also related to the recurrence of adenoma (odds ratio 1.218, 95% confidence interval 1.085−1.368, P = 0.001). However, other factors including age, sex, body mass index, aspirin use, thiazolidinedione use, and follow-up duration did not affect the recurrence of adenoma (Table 6). Multivariate Cox regression analysis showed the same result: that metformin use and the number of baseline adenomas were related to the recurrence of adenoma (Table 7).

The cumulative probability of colorectal adenoma recurrence was significantly lower in the metformin group than in the non-metformin group (log rank test, P = 0.001; Fig. 2). After adjusting for confounding factors, the cumulative recurrence rate of colorectal adenoma in the metformin group was also significantly lower than that in the non-metformin group (Cox proportional hazard model, P = 0.006; Fig. 3).

Table 6. Logistic regression analysis of valuable factors for colorectal adenoma recurrence

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Use of metformin	0.469	0.269-0.816	0.007	0.433	0.256-0.732	0.002
Age	0.983	0.949-1.019	0.349	0.983	0.949-1.019	0.349
Sex	0.692	0.374-1.281	0.242	0.692	0.376-1.271	0.235
Body mass index	0.953	0.873-1.041	0.286	0.959	0.879-1.046	0.344
DM duration	1.178	0.916-1.321	0.277	1.180	0.883-1.299	0.282
Aspirin use	1.597	0.916-2.786	0.099	1.518	0.899-2.563	0.118
Insulin use	1.697	0.654-4.404	0.277	1.793	0.714-4.502	0.214
Thiazolidinedione use	1.961	0.746-5.155	1.172	1.972	0.713-5.180	1.181
Hba1c	1.212	0.842-1.517	0.276	1.292	0.813-1.603	0.281
Number of baseline adenomas	1.211	1.071-1.371	0.002	1.218	1.085-1.368	0.001
Time to first follow- up colonoscopy	1.000	0.999-1.000	0.216	1.000	0.999-1.000	0.212

DM, diabetes mellitus, Hba1c, glycated hemoglobin; HR, hazard ratio; CI, confidence interval

Table 7. Cox regression analysis of valuable factors for colorectal adenoma recurrence

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Use of metformin	0.541	0.369-0.795	0.002	0.572	0.385-0.852	0.006
Age	1.002	0.978-1.027	0.855	0.999	0.974-1.026	0.957
Sex	0.661	0.426-1.028	0.066	0.690	0.442-1.076	0.101
Body mass index	0.972	0.917-1.030	0.339	0.982	0.923-1.045	0.576
DM duration	1.201	0.921-1.302	0.281	1.312	0.902-1.311	0.302
Aspirin use	1.146	0.803-1.636	0.452	1.036	0.714-1.503	0.852
Insulin use	1.256	0.719-2.194	0.437	1.390	0.781-2.475	0.263
Thiazolidinedione use	1.394	0.767-2.536	0.276	1.837	0.991-3.405	0.093
Hba1c	1.153	0.891-1.493	0.280	1.161	0.893-1.508	0.264
Number of baseline adenomas	1.224	1.149-1.313	0.002	1.223	1.147-1.316	0.004

DM, diabetes mellitus, Hba1c, glycated hemoglobin; HR, hazard ratio; CI, confidence interval

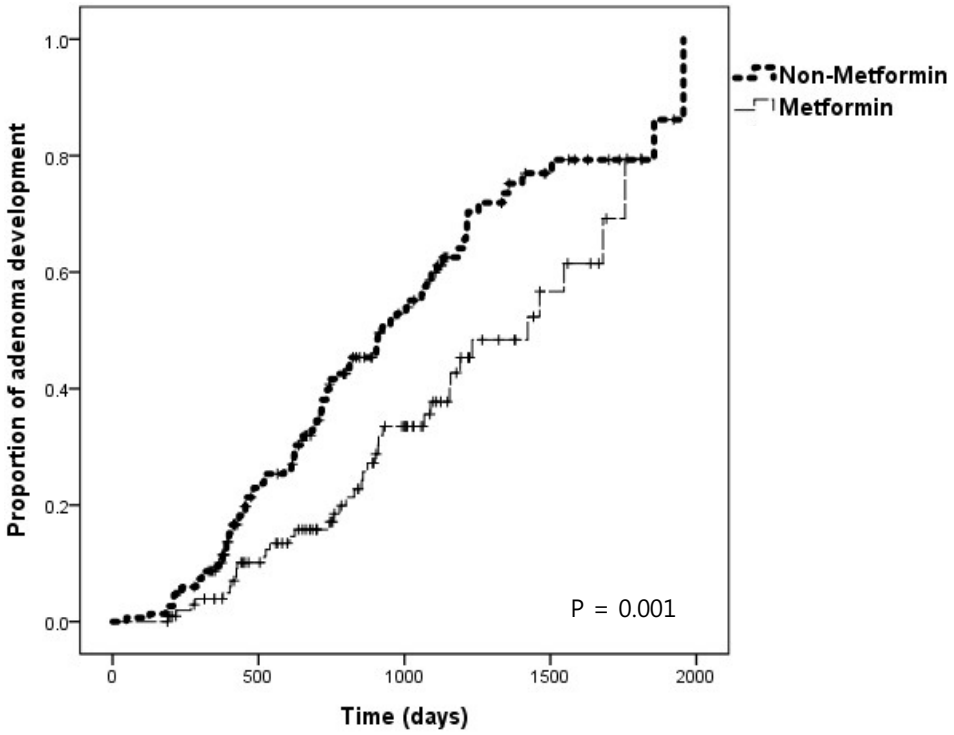

Figure 2. Cumulative recurrence rate of colorectal adenoma

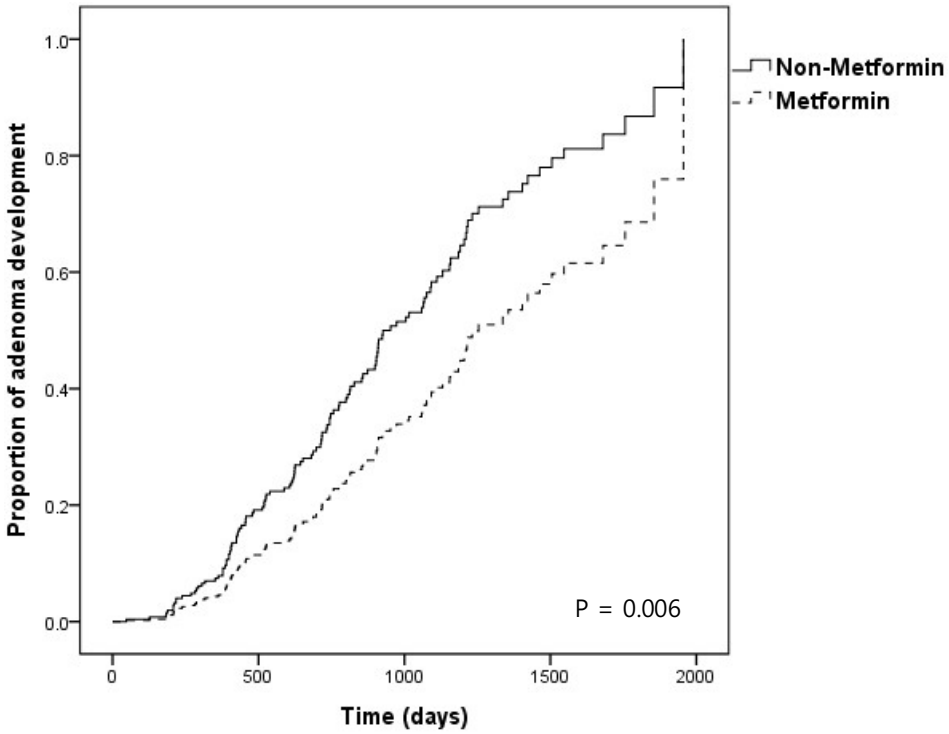

Figure 3. Cumulative recurrence rate of colorectal adenoma after adjusting related factors

IV. DISCUSSION

We found that diabetic patients who took metformin had a lower recurrence rate of colorectal adenoma than those who did not take metformin. In addition, metformin use was associated with a lower cumulative rate of colorectal adenoma recurrence after adjustment for age, sex, body mass index, diabetes mellitus duration, aspirin use, insulin use, thiazolidinedione use, HbA1c, number of baseline adenomas, and time to first follow-up colonoscopy in diabetic patients with previous colorectal adenoma.

Recent studies have shown that diabetes is associated with increased risks of colorectal adenoma and adenocarcinoma.[20,21] Therefore, the potential preventive effect of metformin against colorectal adenoma contributes to a lower incidence of colorectal adenoma and adenocarcinoma in patients with diabetes. Moreover, on the basis of the accumulated evidence on dosage and safety, metformin has the potential for use as a chemopreventive agent for the general population.

In this study, the metformin group showed higher body mass index, higher HbA1c, and lower insulin use. We believe that the reason for these differences is that metformin is usually used as first-line therapy for diabetes and is preferred in obese patients. Because these could be important factors that can affect the development of adenoma and cancer, we included these factors in the adjustment for confounding factors. Our univariate and multivariate logistic regression analyses showed no association between those factors and the recurrence of adenoma.

In the aspect of adenoma recurrence, the metformin group showed lower

recurrence of total adenoma. However, there was no significant difference in the recurrence of advanced adenoma. Our previous study about the effect of metformin on the recurrence of colorectal adenoma in diabetic patients with previous colorectal cancer showed similar results.[18] These results suggest that metformin might suppress the early steps in the adenoma-carcinoma sequence, before the adenoma becomes an advanced adenoma. Therefore, more data from a larger cohort or population with a long-term surveillance duration are needed to confirm the long term effect of metformin on advanced adenoma and CRC.

In the subgroup analysis according to sex, we found that there was a significant difference in the recurrence of total adenoma between metformin users and non-users among male patients but not among female patients. Although the number of female patients was too small for an exact evaluation, hormonal (e.g., estrogen) differences could be related factors in the sex-dependent difference of adenoma recurrence according to metformin use.[22]

In addition, as combined anti-diabetic drugs, we analyzed the use of thiazolidinedione, which has a chemopreventive effect, and insulin, which is related to tumor growth in colorectal cancer. Takahashi et al. reported PPARgamma agonist, an anti-diabetic drug, as a promising candidate for colorectal cancer chemoprevention in their pilot study.[23] Moreover, there are some reports about the effect of thiazolidinedione on decreased risk and mortality of other types of cancer. Meanwhile, a high level of insulin is related to tumor growth and carcinogenesis.[24] Therefore, we included the use of thiazolidinedione and insulin into the multivariate analysis. Although our data did not show a significant association of these two drugs with adenoma recurrence, we could not perform

meaningful analysis owing to the small number of patients taking these two drugs.

As for the aspirin, a well-known chemopreventive drug for colorectal adenoma and cancer did not affect the recurrence of adenoma in our analysis of factors affecting the recurrence rate of colorectal adenoma. We surmise that this different result might be because of the small number of patients taking aspirin and the specific study cohort, in which all patients have diabetes and a significant proportion of whom take metformin.

This study has several limitations. First, this study is retrospective in nature, which means unexpected bias cannot be completely ruled out. We did not have data on noncompliance to metformin treatment, which could have resulted in exposure misclassification and biased results. Additional study limitations included the small sample size, which reduced the power of detecting significant differences in adenoma recurrence, although our findings showed significant results. Finally, because the data analyzed in this study population were collected from a tertiary medical care unit, the results may not be generalizable to the general population. Furthermore, because this study included patients with diabetes, it is difficult to generalize the chemopreventive effect of metformin patients without diabetes.

Recently, a multi center double-blinded placebo-controlled trial was reported by Takuma et al. Their study demonstrated that metformin reduced the prevalence and number of adenomas in non-diabetic patients.[25,26] However, the sample size of the study was small and the follow-up duration was only 1 year. Therefore, to generalize the results, long-term clinical trials with larger samples involving diverse populations are needed. In addition, like our study, more

retrospective data from a diverse population with a long-term follow-up duration could be helpful for designing and performing future large-scale prospective studies.

V. CONCLUSION

Metformin use in diabetic patients has a potential chemoprevention effect against colorectal adenoma. To generalize the use of metformin for the prevention of colorectal adenoma, a large-scale randomized controlled trial with a long term follow-up duration is needed.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Morson B. President's address. The polyp-cancer sequence in the large bowel. Proc R Soc Med 1974;67:451-7.
3. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759-67.
4. Citarda F, Tomaselli G, Capocaccia R, Barcherini S, Crespi M, Italian Multicentre Study G. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001;48:812-5.
5. Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 2009;10:501-7.
6. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891-9.
7. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006;355:885-95.
8. Drazen JM. COX-2 inhibitors--a lesson in unexpected problems. N Engl J Med 2005;352:1131-2.

9. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103-23.

10. Campbell PT, Deka A, Jacobs EJ, Newton CC, Hildebrand JS, McCullough ML, et al. Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. Gastroenterology 2010;139:1138-46.

11. Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 2005;310:1642-6.

12. Hosono K, Endo H, Takahashi H, Sugiyama M, Uchiyama T, Suzuki K, et al. Metformin suppresses azoxymethane-induced colorectal aberrant crypt foci by activating AMP-activated protein kinase. Mol Carcinog 2010;49:662-71.

13. Algire C, Amrein L, Zakikhani M, Panasci L, Pollak M. Metformin blocks the stimulative effect of a high-energy diet on colon carcinoma growth in vivo and is associated with reduced expression of fatty acid synthase. Endocr Relat Cancer 2010;17:351-60.

14. Mei ZB, Zhang ZJ, Liu CY, Liu Y, Cui A, Liang ZL, et al. Survival benefits of metformin for colorectal cancer patients with diabetes: a systematic review and meta-analysis. PLoS One 2014;9:e91818.

15. Rokkas T, Portincasa P. Colon neoplasia in patients with type 2 diabetes on metformin: A meta-analysis. Eur J Intern Med 2016;33:60-6.

16. Cho YH, Ko BM, Kim SH, Myung YS, Choi JH, Han JP, et al. Does metformin affect the incidence of colonic polyps and adenomas in

patients with type 2 diabetes mellitus? Intest Res 2014;12:139-45.

17. Kim YH, Noh R, Cho SY, Park SJ, Jeon SM, Shin HD, et al. Inhibitory effect of metformin therapy on the incidence of colorectal advanced adenomas in patients with diabetes. Intest Res 2015;13:145-52.

18. Lee JH, Jeon SM, Hong SP, Cheon JH, Kim TI, Kim WH. Metformin use is associated with a decreased incidence of colorectal adenomas in diabetic patients with previous colorectal cancer. Dig Liver Dis 2012;44:1042-7.

19. Winawer SJ, Fischer SE, Levin B. Evidence-Based, Reality-Driven Colorectal Cancer Screening Guidelines: The Critical Relationship of Adherence to Effectiveness. JAMA 2016;315:2065-6.

20. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. World J Gastroenterol 2015;21:6026-31.

21. Luo S, Li JY, Zhao LN, Yu T, Zhong W, Xia ZS, et al. Diabetes mellitus increases the risk of colorectal neoplasia: An updated meta-analysis. Clin Res Hepatol Gastroenterol 2016;40:110-23.

22. Singh S, Langman MJ. Oestrogen and colonic epithelial cell growth. Gut 1995;37:737-9.

23. Takahashi H, Hosono K, Uchiyama T, Sugiyama M, Sakai E, Endo H, et al. PPARgamma Ligand as a Promising Candidate for Colorectal Cancer Chemoprevention: A Pilot Study. PPAR Res 2010;2010.

24. Baserga R, Peruzzi F, Reiss K. The IGF-1 receptor in cancer biology. Int J Cancer 2003;107:873-7.

25. Higurashi T, Hosono K, Takahashi H, Komiya Y, Umezawa S, Sakai E, et al. Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicentre double-blind, placebo-controlled, randomised phase 3 trial. Lancet Oncol 2016;17:475-83.

26. Higurashi T, Takahashi H, Endo H, Hosono K, Yamada E, Ohkubo H, et al. Metformin efficacy and safety for colorectal polyps: a double-blind randomized controlled trial. BMC Cancer 2012;12:118.

ABSTRACT (IN KOREAN)

메포민이 대장선종을 절제한 당뇨환자에서 대장선종의 재발에 미치는 영향 분석

<지도교수 김태일>

연세대학교 대학원 의학과

한 민 석

메포민의 복용이 대장암 환자의 예후와 대장암 발생에 긍정적인 영향이 있다는 것은 이미 알려져 있다. 하지만 메포민이 대장암의 전구인 대장 선종에 미치는 영향에 대해서는 아직 알려진 자료가 적다. 따라서 본 연구는 대장 선종을 절제한 당뇨환자에서 메포민 복용이 대장 선종의 재발에 미치는 영향을 분석해 보고자 하였다. 2005년부터 2011년까지 대장 선종 절제를 받고 다시 추적 대장 내시경을 시행 받은 423명의 환자를 대상으로 연구를 진행하였으며, 최종적으로 257명의 환자가 분석되었다.

메포민을 복용 중인 106명의 환자에서 38명(35.8%)이 대장선종의 재발을 보였으나, 메포민을 복용하지 않는 151명의 환자에서는 85명(56.3%)이 대장선종의 재발을 보였다 (P = 0.001). 대장 선종의 재발에 영향을 미치는 인자에 대한 Cox 다변량 분석에서

메포민의 복용은 대장 선종의 재발을 감소시키는 유의한 인자로 확인되었다 (Hazard ratio 0.572, 95% Confidence interval 0.385-0.852, P = 0.006). 또한 메포민을 복용한 군이 메포민을 복용하지 않는 군에 비해 대장 선종의 누적 재발 가능성도 유의하게 낮았다 (P = 0.001).

이상의 결과로 당뇨환자에서 메포민의 복용은 대장 선종의 재발을 억제하는 효과가 있음을 시사한다.

핵심되는 말: 메포민, 대장 선종, 재발, 당뇨