

# Korean Type 2 Diabetes Patients have Multiple Adenomatous Polyps Compared to Non-diabetic Controls

Sunghwan Suh<sup>1</sup>, Mira Kang<sup>2</sup>,  
Mi Yeon Kim<sup>1</sup>, Hye Soo Chung<sup>1</sup>,  
Soo Kyong Kim<sup>1</sup>, Kyu Yeon Hur<sup>1</sup>,  
Jae Hyeon Kim<sup>1</sup>, Myung-Shik Lee<sup>1</sup>,  
Moon Kyu Lee<sup>1</sup> and Kwang-Won Kim<sup>1</sup>

<sup>1</sup>Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; <sup>2</sup>Center for Health Promotion, Samsung Medical Center, Seoul, Korea

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Address for Correspondence:  
Kwang-Won Kim, MD

Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea

Tel: +82-2-3410-3430, Fax: +82-2-3410-3849  
E-mail: kw1234@skku.edu

We tested the correlation between diabetes and aggressiveness of colorectal polyps in diabetic patients and matched non-diabetic controls. We retrospectively studied 3,505 type 2 diabetes (T2DM) patients without gastrointestinal symptoms who underwent colonoscopy for colorectal cancer at Samsung Medical Center, Seoul, Korea from August 1995 to August 2009. We matched 495 non-diabetic subjects with colon polyps to the diabetic patients in whom polyps were detected by year of colonoscopy, age, sex and body mass index (BMI). Among the 3,505 T2DM patients screened, 509 were found to have 1,136 colon polyps. Those with diabetes had a greater proportion of adenomatous polyps (62.8% vs 53.6%) compared to the control. Multivariate logistic regression analysis identified DM, male gender, age and BMI as independent risk factors for multiple polyps (more than three polyps). Polyp multiplicity in diabetic patients was significantly associated with male gender (OR 2.360,  $P=0.005$ ), age (OR 1.033,  $P=0.005$ ) and BMI (OR 1.077,  $P=0.028$ ). Neither aspirin nor metformin use affected either size or number of polyps in diabetic patients. Male patients older than 65 yr with T2DM and BMI greater than 25 have increased risk for multiple adenomatous polyps and should be screened with colonoscopy to prevent colorectal cancer.

**Key Words:** Diabetes Mellitus; Colonic Polyps; Colorectal Neoplasms

## INTRODUCTION

Diabetes mellitus (DM) is a serious and growing health problem worldwide and is associated with severe acute and chronic complications. The industrialization and economic growth accompanied by the so-called 'westernization' of lifestyle, characterized by a high-calorie diet, obesity and physical inactivity may explain this diabetes epidemic. As a result of this change, the mortality of lifestyle-related diseases such as cancer, diabetes and cardiovascular disease has increased in many countries including Korea. Worldwide, cancer is the second leading cause of death and diabetes is the 12th (1). According to Statistics Korea report of 2009 (2), cancer is the leading cause of death in Korea and DM is the 5th most common cause of death. In Korea, the incidence and mortality of colorectal cancer have risen steadily, and now positioned at the 4th most common type of cancer (2) following malignancies of the lung, liver and stomach. Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for various cancers (3) because they share common risk factors such as age, obesity and physical inactivity. A recent meta-analysis associates diabetes with a relative risk of 1.29-1.36 for cancers of colon and rectum (4). In addition to its role as an independent risk factor for tumor development, dia-

betes may influence cancer prognosis. Several studies show that diabetes increases risk for cancer mortality (5, 6).

Screening of colorectal cancer is important because 80% of these cancers are believed to arise from adenomatous polyps that progress from severe dysplasia to invasive carcinoma (7). Therefore, discovery and removal of these precursor lesions can decrease the colorectal cancer incidence by 76% to 90% (8).

Although the link between diabetes and colorectal cancer is well established, few studies have addressed the association between diabetes and colon polyps. In this study, we tested the correlation between diabetes and aggressiveness of colorectal polyps in diabetic patients and matched them with non-diabetic controls for the first time.

## MATERIALS AND METHODS

### Study population

We performed a retrospective study of consecutive type 2 diabetes (T2DM) patients without any gastrointestinal symptoms who underwent colonoscopic screening for colorectal cancer at the Diabetes Center, Samsung Medical Center in Seoul, Korea, from August 1995 to August 2009. We have chosen colonoscopy instead of fecal occult blood test and sigmoidoscopy for the fol-

lowing reason. Flexible sigmoidoscopy can only identify lesions in the distal 60 cm of the bowel and abnormal findings in the distal bowel require colonoscopy for visualization of the entire colon. On the other hand, colonoscopic examination showed the highest effectiveness for screening colon cancer (9) because the procedure can visualize the entire colon and lesions can be removed at the same time. The exclusion criteria included a history of colonic disease, such as colitis, polyps, or cancer; prior colonic surgery or colon polypectomy, and medical history of severe hematologic or connective disorders or other malignancies. The criteria for type 2 diabetes mellitus (T2DM) included symptoms of DM (polyuria, polydipsia or unexplained weight loss) plus a random plasma glucose concentration of at least 200 mg/dL; a fasting plasma glucose level of 126 mg/dL or higher; and a 2-hr plasma glucose level of 200 mg/dL or higher during an oral glucose tolerance test.

### Data collection

Of the 3,505 T2DM patients screened (2,528 men and 977 women), 509 (417 men and 92 women) were found to have colon polyps. Following colonoscopy with polypectomy was done to these patients. Nine patients did not receive polypectomy because they were receiving continuous anti-coagulation medication (such as aspirin or warfarin) at the time of the procedure. The non-diabetic subjects with colon polyps were matched with the 509 diabetic patients with polyps for characteristics (year of colonoscopy, age, sex and body mass index) to clarify the impact of DM on colon polyp. The non-diabetic control subjects with polyps (i.e., without history of DM diagnosis or medication and HbA1c < 5.7%) were pooled from the database of the Center for Health Promotion, Samsung Medical Center. Excluding those with discordances in the year of the procedure, age and sex, 34,628 persons were eligible for matching and from these, 495 were selected by use of a statistical matching tool. We retrospectively evaluated medical records of each patient for data on fasting serum glucose, HbA1c, duration of diabetes, C-peptide, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein and history of aspirin and metformin use at the time of colonoscopy. The pathology database at Samsung Medical Center was interrogated to provide information on all pa-

**Table 1.** Clinical characteristics of diabetic patients with or without colon polyps

Parameters	No polyp (n = 2996)	Polyp (n = 509)	P value
Sex (M/F)	2,111 (70.5%)/ 885 (29.5%)	417 (81.9%)/ 92 (18.1%)	< 0.001
Age (yr)	53.86 ± 9.62	55.98 ± 9.06	< 0.001
DM duration (yr)	6.24 ± 4.44	6.40 ± 4.32	0.455
BMI (kg/m <sup>2</sup> )	24.95 ± 2.90	25.01 ± 3.03	0.714
HbA1c (%)	7.08 ± 1.75	7.00 ± 1.39	0.226
Fasting plasma glucose (mg/dL)	139.92 ± 52.21	135.44 ± 43.64	0.038
C-peptide (ng/mL)	2.41 ± 1.20	2.41 ± 1.17	0.957

DM, Diabetes mellitus; BMI, body mass index.

tients who had removed polyps between August 1995 and August 2009. The aggressiveness of colorectal polyps was measured by polyp size, and number of polyps. Polyps with size greater than 10 mm or number more than three were defined as aggressive polyp (10). Data on lifestyle habits such as smoking, alcohol consumption and physical activity were unavailable.

### Statistical analysis

Statistical analysis was performed using PASW Statistics 18.0 for Windows (SPSS Inc., IL, USA). All data were summarized as the mean ± standard deviation or number and percent. For all statistical analyses, a two-sided P value of < 0.05 was considered significant. The chi-square test was used to compare the differences in variables between the two groups. The Mann-Whitney test and Spearman's correlation analysis were used to test correlations of variables with size and number of colon polyps. All variables that resulted in P value < 0.05 in univariate analysis were entered into a logistic regression analysis to assess the independent association between risk factors and the size and number of polyps.

### Ethics statement

The institutional review board of the Samsung Medical Center, Seoul, Korea approved this study protocol (2010-11-069-001). Informed consent was exempted by the board due to the retrospective design.

## RESULTS

### Diabetic patients with or without polyps

Among 3,505 patients with T2DM who underwent colonoscopy, 509 were found to have 1,136 colon polyps. Characteristics of diabetic patients with or without colon polyps are summarized in Table 1. Compared to the subjects without polyps, those with polyps were older and had lower fasting plasma glucose levels and were more likely to be male.

**Table 2.** Baseline characteristics of diabetic and non-diabetic groups with colon polyps

Parameters	T2DM patients	Non-diabetic controls	P value
Sex (M/F)	417/92	407/88	0.935
Age (yr)	55.98 ± 9.06	55.83 ± 8.56	0.782
Polyp size (mm)	5.80 ± 4.43	4.54 ± 3.88	< 0.001
Polyp number	2.23 ± 1.81	1.54 ± 1.08	< 0.001
Large polyps	81 (15.9%)	41 (8.3%)	< 0.001
Multiple polyps	144 (28.3%)	59 (11.9%)	< 0.001
BMI (kg/m <sup>2</sup> )	25.01 ± 3.03	24.70 ± 2.75	0.089
HbA1c (%)	7.00 ± 1.39	5.21 ± 0.30	< 0.001
Fasting plasma glucose (mg/dL)	135.44 ± 43.64	92.15 ± 9.68	< 0.001

Data are shown as means ± SD or number (percent). T2DM, type 2 diabetes; Polyp size, Largest polyp per individual; Large polyp, polyps with size ≥ 10 mm; Multiple polyps, polyp number more than three; BMI, body mass index.

### Diabetic and non-diabetic groups with colon polyps

Baseline characteristics of 495 matched non-diabetic control subjects with colon polyp are shown in Table 2. Polyp size indicates size of the largest polyp found in an individual. Polyps in diabetic patients were larger and more numerous than the ones in non-diabetic subjects, even though the two groups did not differ significantly in gender, age and body mass index (BMI). Moreover, percentage of aggressive polyp was higher in diabetic patients (15.9 vs 8.3 and 28.3 vs 11.9, respectively). All polyps were removed during endoscopy and examined histologically except in 10 subjects (9 with diabetes and one control) who were taking anti-platelet agents at the time of the procedure (Table 3). The proportion of adenomatous polyps was greater in diabetic than in non-diabetic subjects (62.8% vs 53.6%) but the proportion of adenocarcinoma did not differ significantly between these groups.

### Risk factors for aggressive polyps

Multivariate logistic regression analysis identified DM, male gender, age and BMI as independent risk factors for multiple (more than three) polyps (Table 4). No independent risk factor for polyp size was identified among the patients with diabetes (data not shown). However, multiple polyps in the diabetic patients were significantly associated with male gender (OR 2.360, 95%

CI 1.303-4.276,  $P = 0.005$ ), age (OR 1.033, 95% CI 1.010-1.057,  $P = 0.005$ ) and BMI (OR 1.077, 95% CI 1.008-1.151,  $P = 0.028$ ). As a practical guide to evaluation, the OR was calculated by quartile for age and BMI (Table 5). Male diabetic patients with age  $\geq 65$  and BMI  $\geq 25$  were at risk for having multiple polyps. No independent risk factor for multiple polyps emerged from data for the non-diabetic controls (data not shown). Through a retrospective chart review we determined that 26.7% (136/509) and 29.9% (152/509) of the diabetic patients were taking aspirin or metformin, respectively, at the time of colonoscopy. However, neither medication was correlated with the size or the number of polyps observed (data not shown).

### DISCUSSION

This study confirmed an association between diabetes and multiplicity of colon polyps for the first time. Diabetic patients also had more aggressive and adenomatous polyps than the non-diabetic controls, which may indicate higher risk of progression to colorectal cancer.

A polyp of colon is a focal protuberance into the lumen from the normally flat colonic mucosa. The prevalence rate of polyps is known to be 20% to 40%. Among the 3,505 patients in our study, 509 (14.5%) were found to have colon polyps. This prevalence rate was not higher than the rate in the previous screening studies and was lower than other studies in Asian countries (11-13). This result may reflect the shortcoming of our study to a single-center population. Age and male gender are known to represent significant risk factors for polyps (14-17) and these associations are held true in our diabetic patients. Although diabetic patients with polyps had slightly lower fasting plasma glucose ( $P = 0.038$ ), their average HbA1c (about 7%) did not differ significantly from the level of those without polyps. The prevalence of polyps in DM patients did not differ significantly with respect to fasting plasma glucose ( $\geq 154$  mg/dL vs  $< 154$  mg/dL) or HbA1c (HbA1c  $\geq 7\%$  vs HbA1c  $< 7\%$ ) (data not shown).

Diabetic patients had larger polyps with greater multiplicity, but the prevalence rate of adenocarcinoma was similar in both

**Table 3.** Colorectal polyp histology in diabetic and non-diabetic subjects

Pathology	T2DM patients (n = 509)	Non-diabetic controls (n = 495)
Total polyp number*	1,136	760
Tubular adenoma	701 (61.7%)	397 (52.2%)
Tubulovillous adenoma	7 (0.6%)	9 (1.2%)
Villous adenoma	5 (0.4%)	1 (0.1%)
Hyperplastic polyp	235 (20.7%)	228 (30%)
Inflammatory polyp	26 (2.3%)	8 (1.1%)
No pathologic alteration	112 (9.9%)	69 (9.1%)
Adenocarcinoma	6 (0.5%)	3 (0.4%)
Others <sup>†</sup>	30 (2.6%)	44 (5.8%)
No polypectomy	14 (1.2%)	1 (0.1%)

Data are shown as number (percent). \*Total number of polyps found in each group; <sup>†</sup>Pathologic findings other than previously described.

**Table 4.** Multivariate logistic regression analysis of variables for multiple (more than three) polyps

Variables	OR	95% CI	P value
Male	3.580	2.034-6.300	< 0.001
Diabetes	2.847	1.828-4.436	< 0.001
Age	1.033	1.013-1.053	0.001
BMI	1.066	1.008-1.128	0.026
TC	0.999	0.994-1.004	0.576
HDL	1.000	0.986-1.015	0.976
TG	1.001	0.999-1.003	0.281
Fasting plasma glucose	0.998	0.992-1.004	0.439
HbA1c	1.049	0.869-1.266	0.618

BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglyceride.

**Table 5.** Analysis of risk factors for multiple polyps in diabetic patients

Variables	OR	95% CI	P value
Sex			
Female	1		
Male	2.276	1.261-4.108	0.006
Age			
< 65	1		
$\geq 65$	2.081	1.289-3.359	0.003
BMI			
< 20	1		
20 $\leq$ BMI < 25	6.062	0.784-46.899	0.084
25 $\leq$ BMI < 30	7.739	0.999-59.951	0.050
$\geq 30$	9.422	1.074-82.673	0.043

BMI, body mass index.

groups. Increasing polyp size, a higher number of polyps, villous histology and high-grade dysplasia are risk factors for focal cancer within an individual adenoma (18). Number and size are the most consistent risk factors for metachronous adenomas including advanced adenomas and cancer. In general, polyps with size more than 10 mm or number more than three are known as high risk for colorectal cancer (9). The proportion of these aggressive polyps was higher in T2DM patients (Table 2). Moreover, adenomatous polyp, a premalignant lesion that tends to progress into colorectal cancer via the traditional adenoma-carcinoma sequence, was more common in the diabetic group than in the non-diabetic control group (Table 3). A multivariate logistic regression analysis of our data identified diabetes, male gender, age and BMI as independent risk factors for multiple (more numerous than three) polyps. Interestingly, serum fasting glucose and lipid levels were not associated with polyp size or number. The influence of these factors was probably minor, if any and may have been obscured by the significantly larger (2.85-fold) impact of diabetes on polyps in the multivariable analysis (Table 4).

In testing variables as independent risk factors for polyp aggressiveness in diabetic subjects, we found that none was associated with polyp size. However, multiple polyps were significantly associated with male gender (OR 2.360, 95% CI 1.303-4.276,  $P = 0.005$ ), age (OR 1.033, 95% CI 1.010-1.057,  $P = 0.005$ ) and BMI (OR 1.077, 95% CI 1.008-1.151,  $P = 0.028$ ). For clinical guidance, we analyzed OR for age and BMI by quartile, and found that diabetic patients with age  $\geq 65$ , BMI  $\geq 25$  and male gender were more likely to have multiple polyps (Table 5). From these results, we can speculate that diabetes have influence on the number of polyps although not on the size reflecting its effect on polyps' formation not their development. Chronic hyperinsulinemia may favor cancer initiation and progression in diabetic patients due to the mitogenic effect of insulin (19). Prospective epidemiologic studies of biomarkers of insulin resistance show that individuals with higher insulin levels are at higher risk for colon cancer (20). Rather than measuring serum insulin levels, we measured C-peptide, because some of the patients enrolled in this study were using insulin to control diabetes. However, C-peptide levels were not correlated with polyp-related variables (i.e. size and number) in our study, which may stem from the small number of patients in our study as compared to the larger ones. A 10-yr prospective cohort study of 1.3 million Koreans aged 30 to 95 yr showed that serum glucose concentration was strongly associated with colon cancer (5). However, we did not find a relationship between HbA1c or serum glucose level and characteristics of colon polyps. This finding may be explained by rather good control of plasma glucose (HbA1c around 7%) in our study. Kim et al. (21) also reported that increased serum fasting glucose was not associated with the development of colon adenoma in metabolic syndrome subjects. Moreover, subgroup analysis in our study failed to correlate fasting plasma glu-

cose and HbA1c levels with colon polyp multiplicity or size. The absence of association between metabolic risk factors and polyps may be due to a narrower range of values of metabolic variables, which could have been influenced by patient medication. This implies that diabetes itself, although in good control, is associated with multiplicity of colon polyps. Diabetes is a complex metabolic disorder and hyperglycemia alone may not explain all of its deleterious effects on polyps. Usually by the time a diagnosis of diabetes is made, endogenous hyperinsulinemia has been maintained for a significant period time, even as pancreatic beta-cell function starts to decline. Eventually, decreased beta-cell function becomes unable to overcome insulin resistance and exogenous insulin therapy is required. Thus, T2DM patients may have longer exposure to hyperinsulinemia than to hyperglycemia. However, these hypothetical mechanisms await further study.

Numerous studies confirm an inverse association between aspirin use and risk of colorectal cancer (22). A mounting body of evidence suggests that metformin may also reduce cancer risk in diabetic patients (23). In this study, however, neither regular aspirin nor metformin use showed any effect on clinical behavior of the polyps. Siddiqui et al. (24) also failed to find the association between aspirin use and polyp characteristics in T2DM patients. The preventive role of aspirin to colorectal cancer is strongly associated with higher dosage ( $\geq 500$  mg daily) and longer duration ( $\geq 10$  yr) of use (25). Low-dose aspirin use to reduce cardiovascular risks in diabetic patients may fall short of a protective role in cancer. Metformin use to protect against colorectal polyp should be tested further in a large long-term prospective study.

We attempted to balance the limitations in this study with corresponding advantages. Although subjects in this study were selected from a single-center population, we matched diabetic and non-diabetic subjects by contrast to clarify by contrast the effects of diabetes on colon polyps. Data on lifestyle habits such as smoking, alcohol consumption and physical activity were excluded by the retrospective design. On the other hand, this study had the methodological advantage that colonoscopy was done for all subjects found to have polyps leaving no hidden ones. To our knowledge, this is the first study to compare characteristics of colon polyps in matched diabetic and non-diabetic subjects.

In conclusion, male T2DM patients older than 65 yr and BMI more than 25 have increased risk for multiple adenomatous polyps. These individuals should be encouraged to undergo screening with colonoscopy to prevent colorectal cancer.

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## AUTHOR SUMMARY

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