

# Insulin levels are associated with risk of colon adenoma and not nonadenomatous polyps

## A retrospective, hospital-based study

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### Abstract

Recently, the prevalence of colorectal cancer has been increasing in Korea. Several studies have reported that adenomatous polyps, known as precancerous lesions, are associated with increased blood insulin levels. The principal objective of the present study was to examine the correlation between insulin levels and colon polyps in subjects without a history of diabetes or colorectal cancer. From January 2, 2018 to December 31, 2019, 3277 adults who visited the University Hospital Health Examination Center and underwent colonoscopy were included in this study. Insulin, glycated hemoglobin (HbA1c), and fasting blood glucose levels were measured, and past medical history, alcohol consumption, smoking, and physical activity were assessed using self-administered questionnaires. Among the 3277 subjects, the prevalence of adenomatous and nonadenomatous lesions were 22.2% and 11.5%, respectively. The mean values of insulin, HbA1c, and fasting blood glucose were significantly increased in the adenomatous and nonadenomatous polyp groups compared to the normal group. Logistic regression analysis showed that the risk of adenoma (odds ratio [OR] 1.483; 95% confidence interval [CI], 1.170–1.878) and nonadenomatous polyps (OR 1.415; 95% CI, 1.038–1.929) were increased in the high insulin level group ( $\geq 7.36$  uIU/mL), and only the risk of adenoma (OR 1.312; 95% CI, 1.003–1.718) was significantly higher after adjustment for disturbance variables. This study suggests that an increase in insulin levels is a significant risk factor for colon adenoma.

**Abbreviations:** BMI = body mass index, CI = confidence interval, FBG = fasting blood glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, IGF-1 = insulin-like growth factor-1, METs = metabolic equivalent of task, OR = odds ratio, T2DM = type 2 diabetes mellitus, TG = triglyceride.

**Keywords:** colon adenoma, colon polyp, insulin

### 1. Introduction

According to a 2018 report on global cancer incidence, colorectal cancer was the second and third most common cancer in women and men (10.9%), respectively. By region, the incidence is highest in developed countries, such as Europe, Oceania, the United States, and East Asia, and the incidences are rising in semi-developed and developing countries.<sup>[1]</sup> Recently, the incidence of colorectal cancer has been increasing in Korea due to a shift to a westernized diet and increasing use of colonoscopy. According to the 2017 cancer registry data published by the Korea Central Cancer Registry, the prevalence of colorectal cancer is 13.4%, ranking third following thyroid cancer and gastric cancer.<sup>[2]</sup>

Of the various types of colon polyps, colon adenoma, traditionally perceived as an antecedent to cancer,<sup>[3]</sup> and hyperplastic polyps, known to have no malignant potential, were recently reported to progress to malignant polyps via the

serrated neoplastic pathway.<sup>[4]</sup> Colon polyps can be detected and removed through endoscopy, and this can help prevent colorectal cancer.<sup>[5]</sup>

The risk factors for colorectal cancer have been studied extensively, and some risk factors for colorectal cancer and colon polyps include a westernized diet, abdominal obesity, smoking, drinking, and physical inactivity.<sup>[6–8]</sup> It has been reported that the incidence of colon polyps is high among patients with type 2 diabetes mellitus (T2DM) or metabolic syndrome.<sup>[9,10]</sup>

Insulin resistance is a key mechanism underlying the onset of T2DM and metabolic syndrome, and it causes compensatory hyperinsulinemia through abnormal blood glucose responses to endogenous insulin. The hypothesis that elevated insulin concentration and insulin resistance increase the risk of colorectal cancer by increasing the level of insulin-like growth factor-1 (IGF-1) and contributing to carcinogenesis is largely accepted,<sup>[11]</sup> and multiple studies have been performed

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using insulin-related plasma factors and IGF-1 to test this hypothesis.<sup>[12,13]</sup>

Past findings on the association between insulin concentration and the incidence of colorectal cancer and colon adenomas are inconsistent. While some studies showed the existence of an association,<sup>[12,14,15]</sup> others reported that they are not significantly associated<sup>[16–18]</sup>; thus, the association between insulin concentration and the onset of colorectal cancer and colon adenomas remains controversial. Most previous studies have specifically examined adenomas, and there is a paucity of studies on nonadenomatous polyps, including hyperplastic polyps.<sup>[9,14,15]</sup>

Therefore, this study aimed to investigate the association of blood insulin concentration with colon adenomas and nonadenomatous polyps in patients who underwent colonoscopy as part of their health examination at a university hospital.

## 2. Methods

### 2.1. Participants and duration of study

Adults who underwent colonoscopy at the health examination center of a university hospital between January 2018 and December 31, 2019 were included in the study. Of 3571 individuals who underwent insulin, hemoglobin, and fasting glucose tests in addition to colonoscopy, individuals who were currently being treated for DM, individuals with a history of colorectal cancer, individuals diagnosed with colorectal cancer during colonoscopy, and individuals whose entire colon could not be observed due to inadequate bowel preparation were excluded, resulting in a total of 3277 individuals included in the analysis. The Institutional Review Board of Soonchunhyang University Cheonan (SCHCA 2021-07-040) approved this study and waived the informed consent requirement because we used only de-identified information which was routinely collected during health check-up visits.

### 2.2. Method

During colonoscopy, the entire colon up to the ileocecum was observed using a long flexible colonoscope, and a biopsy was performed if colon polyps were discovered. The participants were divided into the adenoma group, nonadenomatous polyp group (hyperplastic polyp and inflammatory polyp), and normal group (no polyps) based on histopathological findings.

Venous blood samples were taken after a minimum of 10 hours of fasting to measure insulin, blood glucose, and hemoglobin levels. Participants' insulin concentration was divided into quartiles: Q1 ( $\leq 3.39$  uIU/ml), Q2 (3.40–4.99 uIU/ml), Q3 (5.00–7.35 uIU/ml), and Q4 ( $\geq 7.36$  uIU/ml).

Body mass index (BMI) was calculated by dividing body weight (kg) by height, in meters, squared ( $m^2$ ) based on measurements taken at the time of hospital visit. Waist circumference was measured using a tape measure around the narrowest part between the lowest rib and iliac crest. On the day of the test, a patient questionnaire was administered to obtain information about underlying diseases such as DM and colorectal cancer, as well as lifestyle factors such as smoking, drinking, and physical activity. Smoking status was classified as never, past smoker, and current smoker, and heavy drinking was defined as consumption of  $\geq 280$  g alcohol in the past week for men and  $\geq 140$  g alcohol in the past week for women.<sup>[19]</sup> Physical activity was classified as moderate (600–2999 metabolic equivalents of tasks [METs]) and high ( $\geq 3000$  METs) by converting the weekly amount of exercise into METs.<sup>[20]</sup>

### 2.3. Statistical analysis

Continuous variables in the general, clinical, and metabolic characteristics, age, BMI, waist circumference, blood pressure,

insulin, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) showed a normal distribution upon application of the Kolmogorov-Smirnov test; accordingly, they were analyzed using 1-way analysis of variance. Categorical variables, namely sex, heavy alcohol consumption, physical activity, and smoking status, were analyzed using chi-square tests to compare between the normal, nonadenomatous polyp, and adenoma groups. The unadjusted risk ratios for colon polyps and variables with differences between polyp groups were analyzed using univariable logistic regression. The differences in the colon polyp groups according to insulin concentration quartiles were analyzed using chi-square tests.

The risk ratios for insulin concentration and colon polyps were analyzed by logistic regression using 3 models: Model 1 was unadjusted; Model 2 was adjusted for sex, age, heavy drinking, smoking status, TG, and HDL-C; and Model 3 was adjusted for significant variables identified in the univariable logistic regression. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (version 25.0; IBM Co., Armonk, NY), and the confidence interval (CI) was set at 95%. A 2-tailed  $P$ -value of  $< .05$  was deemed statistically significant. The post hoc power was calculated as 0.812.

## 3. Results

### 3.1. Participants' characteristics according to polyp type (Table 1)

A total of 3277 participants were reviewed. The mean age was  $38.53 \pm 6.87$  years, and the mean insulin concentration was  $5.92 \pm 3.9$  uIU/mL. A total of 378 (11.5%) and 726 (22.2%) participants were in the nonadenomatous polyp and adenoma groups, respectively.

The insulin concentration was significantly higher in the nonadenomatous polyp group ( $6.48 \pm 4.38$  uIU/mL) and adenoma group ( $6.32 \pm 4.35$  uIU/mL) than in the normal group ( $P < .001$ ). Both groups also had significantly higher HbA1c, FBG, age, and TG than the normal group, and both groups had significantly lower HDL-C levels than the normal group. There were no significant differences in insulin, HbA1c, FBG, TG, and HDL-C between the adenoma and nonadenomatous polyp groups.

The nonadenomatous polyp group consisted of 72.2% men and 27.9% women, while the adenoma group comprised 71.9% men and 28.1% women ( $P < .001$ ). The percentage of current smokers in the nonadenomatous polyp and the adenoma groups was 20.1% and 18.2%, respectively ( $P < .001$ ).

### 3.2. Unadjusted odds ratios and 95% confidence intervals for colon polyps according to clinical characteristics (Table 2)

Male sex, older age, current smoking status and higher TG levels were associated with a significantly higher risk of nonadenomatous polyp and adenoma. Lower HDL levels were associated with a higher risk of nonadenomatous polyps, whereas heavy drinking was associated with a higher risk of adenoma.

### 3.3. Prevalence of colon polyps according to insulin quartiles (Table 3)

Q4 and Q3 insulin concentrations were the most common in the adenoma group (25.8%) and the nonadenomatous polyp group (13.3%), respectively. In the normal group, Q1 (69.9%) was the most common, and Q4 (61.4%) was the least common ( $P < .003$ ).

**Table 1**  
**Clinical characteristics of study subjects.**

Variable	Total (n = 3277)	Normal (n = 2173)	Nonadenomatous polyp (n = 378)	Adenoma (n = 726)	P -value
Sex					<0.001
Male	2087 (63.7)	1292 (59.5)	273 (72.2)	522 (71.9)	
Female	1190 (36.3)	881 (40.5)	105 (27.8)	204 (28.1)	
Age (yr)	38.53 ± 6.87	37.61 ± 6.31*	39.31 ± 6.46†	40.85 ± 7.99‡	<0.001
BMI (kg/m <sup>2</sup> )	24.34 ± 3.60	24.03 ± 3.60	25.11 ± 3.55	24.89 ± 3.47	0.138
SBP (mm Hg)	117.44 ± 11.97	116.76 ± 12.02	119.10 ± 12.12	118.62 ± 11.60	0.351
DBP (mm Hg)	73.20 ± 9.63	72.71 ± 9.57	74.10 ± 10.13	74.21 ± 9.43	0.482
WC (cm)	82.74 ± 10.45	81.62 ± 10.41	85.50 ± 10.15	84.67 ± 10.16	0.301
TG (mg/dL)	131.72 ± 87.96	123.36 ± 84.04*	146.86 ± 88.87†	148.88 ± 95.23‡	<0.001
HDL (mg/dL)	59.64 ± 15.99	60.96 ± 16.07*	55.82 ± 13.60†	57.67 ± 16.38†	0.001
FBG (mg/dL)	94.44 ± 13.03	93.57 ± 12.31*	95.49 ± 14.00†	96.49 ± 14.31†	<0.001
HbA1c (%)	5.44 ± 0.44	5.40 ± 0.42*	5.50 ± 0.45†	5.52 ± 0.49†	0.002
Insulin (uIU/mL)	5.92 ± 3.96	5.69 ± 3.72*	6.48 ± 4.38†	6.32 ± 4.35†	<0.001
Current smoking	445 (13.6)	237 (10.9)	76 (20.1)	132 (18.2)	<0.001
Heavy drinking	432 (13.2)	267 (12.3)	61 (16.1)	104 (14.3)	0.073
Physical activity					0.633
Moderate	1211 (37)	790 (36.4)	147 (38.9)	274 (37.7)	
High intensity	134 (4.1)	93 (4.3)	17 (4.5)	24 (3.3)	

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, WC = waist circumference, TG = triglyceride, HDL = high-density lipoprotein cholesterol, FBG = fasting blood glucose, HbA1c = glycated hemoglobin.

Data are presented as mean ± standard deviation or number(%). P-values are calculated from ANOVA or chi-square test.

\*,

†The same letters indicate non-significant differences between groups in Turkey multiple comparison test.

**Table 2**  
**Unadjusted Odds ratios and 95% confidence intervals for colon polyps according to clinical characteristics.**

Variable	Nonadenomatous polyp	Adenoma
Sex (Male)	1.773 (1.393–2.256)*	1.745 (1.453–2.095)*
Age (yr)	1.040 (1.023–1.057)*	1.067 (1.054–1.080)*
Current smoking	2.592 (1.907–3.522)*	2.287 (1.788–2.926)*
Heavy drinking	1.374 (1.015–1.859)*	1.194 (0.935–1.523)
TG(mg/dL) ≥150	1.932 (1.535–2.430)*	1.783 (1.489–2.136)*
HDL(mg/dL) (Men < 40, Women < 50)	1.266 (0.893–1.796)	1.485 (1.145–1.927)*

TG = triglyceride; HDL = high-density lipoprotein cholesterol.

P-values were calculated using logistic regression analysis.

\*P-value < .05.

**Table 3**  
**Prevalence rates of colon polyps according to insulin quartiles**

	Insulin quartiles (uIU/mL)				P-value
	Q1 (≤3.39)	Q2 (3.40–4.99)	Q3 (5.00–7.35)	Q4 (≥7.36)	
Normal	575 (69.9)	554 (67.5)	542 (66.5)	502 (61.4)	0.003
Nonadenomatous polyp	85 (10.3)	80 (9.7)	108 (13.3)	105 (12.8)	
Adenoma	163 (19.8)	187 (22.8)	165 (20.2)	211 (25.8)	

Values are presented as number (%).

P-values were calculated using the chi-square test.

**3.4. Odds ratio for colon polyp according to insulin quartiles (Table 4)**

For the nonadenomatous polyp group, the unadjusted Model 1 showed a higher OR at Q4 (1.415 95% confidence interval(CI), 1.038–1.929) than the normal group. There were no significant increases in the OR identified in Model 2 or Model 3 (adjusted for sex, age, smoking and TG).

For the adenoma group, the OR was significantly higher in Q4 than in the normal group in Models 1, 2, and 3 (1.483, 95%

CI, 1.170–1.879; 1.312, 95% CI, 1.003–1.718; 1.339, 95% CI, 1.026–1.748, respectively).

**4. Discussion**

Colon polyps are lesions that form in the lining of the colon, excluding visually detectable colon cancer. Most types of colon polyps are adenomas (50–60%) and hyperplastic polyps (10–30%).<sup>[21]</sup> Adenomas progress to colon cancer over a period of

**Table 4**  
Odds ratios and 95% confidence intervals for colon polyps according to insulin quartiles.

	Insulin quartiles (uIU/mL)				AIC	BIC
	Q1 ( $\leq 3.39$ )	Q2 (3.40–4.99)	Q3 (5.00–7.35)	Q4 ( $\geq 7.36$ )		
Nonadenomatous polyp						
Model 1	1.00	0.977 (0.705–1.354)	1.348 (0.991–1.833)	1.415 (1.038–1.929)*	2139.4388	2162.8158
Model 2	1.00	0.939 (0.672–1.311)	1.234 (0.894–1.704)	1.177 (0.832–1.666)	2081.9849	2146.2715
Model 3	1.00	0.938 (0.672–1.310)	1.227 (0.889–1.649)	1.170 (0.830–1.651)	2079.1215	2131.7196
Adenoma						
Model 1	1.00	1.191 (0.936–1.514)	1.074 (0.840–1.374)	1.483 (1.170–1.879)*	3258.9257	3282.8142
Model 2	1.00	1.162 (0.905–1.492)	1.022 (0.786–1.003)	1.312 (1.003–1.718)*	3097.8969	3163.5903
Model 3	1.00	1.164 (0.906–1.495)	1.026 (0.790–1.333)	1.339 (1.026–1.748)*	3095.4051	3149.1542

AIC = Akaike information criterion, BIC = Bayesian information criterion, HDL = high-density lipoprotein cholesterol, TG = triglyceride.

Model 1: unadjusted; Model 2: adjusted for sex, age, alcohol consumption, smoking, TG and HDL; Model 3: adjusted for sex, age, smoking and TG.

P-values were calculated by logistic regression analysis.

\* P-value < .05.

5 to 10 years, and according to a cohort study conducted in the United States, the group of people with a history of high-risk adenoma had a 2.7-fold higher incidence of colon cancer compared to the normal group.<sup>[3]</sup> Hyperplastic polyps, which were previously considered benign polyps, have recently been reported to progress to colon cancer via DNA methylation and DNA repair deficiency.<sup>[22]</sup>

Smoking, drinking, obesity, reduced physical activity, metabolic syndrome, and DM have been identified as risk factors for colon polyps.<sup>[6,7]</sup> These factors share a common mechanism of insulin resistance, which induces an elevated insulin concentration in the blood through abnormal glucose response.<sup>[11]</sup> The varying incidences of colon polyps according to insulin concentration have been examined in numerous studies; however, the results are inconsistent.<sup>[14–18]</sup> In particular, most previous studies have focused on adenomas,<sup>[9,14,15,23,24]</sup> so study data on the effects of insulin on nonadenomatous polyps, such as hyperplastic polyps, are lacking.

In our study, the prevalence of adenoma and nonadenomatous polyps was high among individuals with a high insulin concentration. Hyperinsulinemia, increased insulin resistance, and increased IGF-1 levels play a crucial role in the mechanism underlying the onset of colorectal cancer or adenoma related to insulin concentration.<sup>[14,25–28]</sup> Insulin increases the production and activity of IGF-1 by regulating its synthesis in the liver or restricting the release of inhibitory IGF-1 binding proteins. An elevated IGF-1 level is known to facilitate the development of colorectal cancer by stimulating the growth of normal colonic mucosal cells and inhibiting their apoptosis.<sup>[13,14,29]</sup>

Model 2 in our study was adjusted for smoking, drinking, but this was not significant. A previous study on nonadenomatous polyps in the Japanese population reported that the prevalence of hyperplastic polyps was 1.7 times higher in the high insulin group.<sup>[30]</sup> The study could not provide a plausible theoretical basis for the occurrence of hyperplastic polyps in relation to insulin concentration; however, it hypothesized that it could be associated with a DNA-related mechanism, as mentioned in the introduction. Further studies on the association between insulin concentration and the formation of hyperplastic colon polyps are required.

In the present study, the percentage of smokers was significantly higher in the adenoma and nonadenomatous polyp groups than in the normal group. Cigarettes contain numerous carcinogenic substances, which can reach the colon mucosa through the blood or intestinal tract and induce colon cancer.<sup>[8]</sup> Botteri et al<sup>[31]</sup> reported in their meta-analysis that the risk of colorectal cancer in the smoker group is 1.18 times that in the control group. The FBG and TG components of metabolic syndrome were higher in the adenoma and nonadenomatous polyp groups than in the normal group, while the 2 groups had lower

HDL-C levels than the normal group. Metabolic syndrome is caused by insulin resistance, and a study on a Korean population reported that the risk for adenomas increases by 1.44 times among those with metabolic syndrome.<sup>[32]</sup>

This study had several limitations. First, the causality between insulin concentration and colon polyps could not be determined due to the cross-sectional design. Second, data from individuals who visited the health examination center of only 1 university hospital were used, so the study sample is likely to be biased toward people who show a certain level of interest in their health; thus, the study sample is not representative of the general community population. Third, other factors, such as diet, that may influence insulin concentration or colon polyps, could not be controlled.

However, this study is significant because a relatively large study sample was used, both endoscopic and histopathological findings were analyzed, and nonadenomatous polyps were differentiated from adenomatous polyps in the analysis. In addition, this study observed that insulin concentration was significantly associated with colon polyps even after adjusting for the risk factors for adenomas: sex, age, smoking status, alcohol consumption, and physical activities, as well as FBG, HbA1c, TG, and HDL-C levels.

In conclusion, elevated insulin concentration was not associated with an increased risk of nonadenomatous colon polyps and was only associated with an increased risk of colon polyps in adults without DM. Subsequently, large-scale prospective studies should be performed to elucidate the causal relationship between insulin concentration and colon polyps.

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