Lower Gastrointestinal Colonoscopic Results among Diabetic and Non-Diabetic Patients and their Differences

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ABSTRACT

Objective: Diabetes has become an American Epidemic. Currently 8.3 percent of the US population has diabetes and rates may be as high as 33% by the year 2050. Diabetes is a risk factor for colorectal cancer. An adenoma of the colon is a well-established pre-malignant lesion of colorectal cancer. The aim of this study is to explore the relationship between diabetes, its treatments (Use of metformin) and the development of colorectal adenoma.

Methods: Colonoscopy reports from a total of 66 endoscopists including 41 gastroenterologists, 15 colorectal surgeons, 7 general surgeons and 3 other proceduralists in one big hospital in midwest were reviewed. Colonoscopy findings including quality of preparation, polyp size, location, morphology and pathology were retrieved. Besides colonoscopy finding we collected patient's history of diabetes, metformin treatment.

Results: Of the 7382 colonoscopy reports were reviewed, 3465 average risk patients were included in our final analysis. The pathologically proven Adenoma detection rate **(ADR)** in total population was 24.6 % (30.2% in Men and 19.2% in Women). Mean age of study population was 60.63 ± 9.2. Old age and male sex were significant associated with increasing risk of colorectal adenoma. Diabetes was associated increased risk of colorectal adenoma (Odds' ratio 1.32, 95% confidence interval 1.06-1.66, $p = 0.014 < 0.05$). Total 426 (12.29 %) patients have diabetes in our study. There was no significant difference in risk of adenoma in type-1 and type-2 diabetes.

Conclusion: Diabetic subjects have increased risk of developing colorectal adenoma.

INTRODUCTION

Currently 8.3 percent of the US population has diabetes and these rates may be as high as 33% by the year 2050 [1]. Diabetes mellitus is very complex disease with long term complications that include cardiovascular, retinal, and nerve disease, chronic renal failure and a high tendency for infection. Colorectal cancer is the second leading cause of cancer-related deaths in the United States. In 2007, 142,672 people in the United States were diagnosed with colorectal cancer and 53,219 people died from colorectal cancer [2]. Colon adenomas are pre-malignant lesions of colorectal cancer **(CRC)**. Studies have shown an association between diabetes and colorectal cancer. Common etiological factors for both diseases include obesity, a sedentary lifestyle, and the Western diet. This relationship has led to the hypothesis that there might be a connection between diabetes and CRC, rendering diabetes a contributory factor for CRC [3]. There has been speculation that people with type 1 and type 2 diabetes might be at an increased risk for cancer, however there is more evidence available for subjects with type 2 diabetes [4-6]. The underlying mechanism has been discussed and some studies conclude that it is the result of dysregulation of insulin and insulin-like growth factors **(IGFs)**, the so called IGF axis [7]. Colonoscopy is the preferred colorectal cancer screening modality. It is not only a diagnostic tool but it also has therapeutic value. Early detection and removal of polyps by colonoscopy decreases the incidence and mortality from colorectal cancer [8,9]. Previous epidemiologic studies have shown a relationship between diabetes and colorectal cancer.

Diabetes is a very significant health problem in the US and as it becoming more prevalent daily, with almost 4000 Americans being diagnosed daily [1]. Diabetes is the seventh leading cause of death in the US [1]. Further in 2010, 79 million American adults aged 20 years or older had pre-diabetes. Most of these individuals will develop diabetes [10]. With the prevalence of diabetes and the complexity of this disease, it is important to research the effects of diabetes on different body systems. Diabetes mellitus may be an important risk factor for colorectal cancer but this relationship needs to be evaluated further.

In this study the investigators are exploring the association between type-2 diabetes and colorectal adenoma. We will also analyze the relationship between type-2 diabetes and different features of colorectal adenomas such as location (proximal vs distal), and different pathological types of adenoma. Secondary factors in this study are to evaluate how demographic factors affect the aforementioned association between diabetes and colorectal adenoma (age, gender, smoking, alcohol use, type of diabetes).

Our first hypothesis is that subjects with type-2 diabetes will have an increased risk of developing colorectal adenoma compared to subjects without diabetes (Table 1).

Table 1: Physical characteristic of study population.

Characteristics	All Subjects (n=3465)	Non Diabetic (n=3038)	Diabetic (n=426)	*p*
1. Age	60.63 ± 9.20	60.17 ± 9.11	63.88 ± 9.19	<0.001
2. Sex (male/female)	1697 (49%) / 1767 (51%)	1486/1552	211/215	0.812
3. Smoking				
a. Current smoker (%)	9.7	10.0	7.3	0.080
b. Former smoker (%)	36.0	34.1	49.5	<0.001
c. Never smoker (%)	49.2	50.3	41.3	0.001
4. Alcohol Use (%)	51.9	53.7	39.0	<0.001

ADR-Adenoma Detection Rate, PDR-Polyps Detection Rate, SSPDR-Sessile Serrated Polyps Detection Rate.

MATERIALS AND METHODS

In this retrospective chart review we analyzed subjects above the age of 50 who had undergone a screening complete colonoscopy at the Cleveland Clinic during the years 2008-2009. This included a total of 7382 colonoscopy reports. However, 3917 were excluded for one of the following reasons: incomplete colonoscopy, poor bowel preparation, or a condition that excluded them from analysis (personal history of polyps, CRC, family history of polyps or CRC, prior colonic resection, hereditary colorectal cancer syndrome or inflammatory bowel disease. The colonoscopies at the Cleveland Clinic are performed by a total of 66 endoscopists belonging to the following specialties: gastroenterology, colorectal surgery and general surgery. An average of 51 screening colonoscopies performed by each endoscopist were included and were reviewed for patient demographics, presence of diabetes, type of diabetes, current treatments for diabetes, colonoscopic findings including quality of preparation, polyp characteristics such as size, location, morphology and pathology. This information was extracted through reviewing electronic medical records. All subjects >50 years of age with an average risk for CRC, who had their first, complete colonoscopy with good or excellent bowel preparation were included in the study. The adenoma detection rate **(ADR)** was defined as the percentage of colonoscopies in which at least one adenoma was detected. An adenoma was deemed to be detected when pathology of the polyp confirmed the presence of either tubular adenoma, tubulovillous adenoma **(TVA)**, adenomas with high grade dysplasia **(HGD)** or cancerous polyp. Polyp detection rate **(PDR)** was defined similarly. The proximal colon was defined as the portion of the large bowel inclusive of cecum, ascending colon, transverse colon and splenic flexure. Distal colon was defined as the portion that was inclusive of descending colon, sigmoid colon and rectum. Detection rates of sessile serrated adenomas **(SSADR)** were separately calculated. This study has been approved by Institutional Review Boards of the Ohio University and the Cleveland Clinic.

Statistical Methods

Continuous variables were expressed as mean ± standard deviation. Means and standard deviations for continuous variables and frequencies for categorical factors were calculated. Mean age was compared with a two-sample t test, and the $\chi 2$ test was used to compare categorical variables. Study subjects were categorized according to: age, gender, diabetic versus non diabetic, Type-1 diabetes versus type-2 diabetes, subjects on met form in versus not on met form in, smoking status and alcohol use. Logistic regressions were used to identify the relationship between diabetes and the adenoma detection rate **(ADR)**. ADR, polyps detection rates **(PDR)** and sessile serrated polyps detection rates **(SSPDR)** were differentiated among those with diabetes and those without diabetes using an independent sample t-test. All statistical tests were two-tailed and $\alpha = 0.05$ or less were considered statistically significant. All confidence intervals **(CI)** were reportable at 95%. The data was analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

RESULTS

We looked at all the 7382 colonoscopy reports.. We excluded a total of 3917 subjects from our analysis due to an incomplete colonoscopy, fair or poor bowel preparation, prior colonic resection, personal history of polyps or CRC, family history of polyps or CRC, a hereditary colorectal cancer syndrome or inflammatory bowel disease. Therefore a total of 3465 reports were included in this study. The average age of the analyzed subjects was 60.63 years (SD ± 9.203). There were 1697 men (49%) and 1767 women (51%).

The pathologically proven adenoma detection rate **(ADR)** in the total population was 24.6 % (30.2% in Men and 19.2% in Women). As patient age increased the chance of adenoma detection also increased significantly ($r = 0.045$, $p = 0.008$). Males were 1.8 times more likely to associate with adenoma detection than females (odds ratio = 1.813, 95% CI, 1.55-2.12). Those subjects who never smoked were associated with decreased risk of colorectal adenoma, while current and former smoking behaviors were not statistically significantly associated with developing colorectal adenoma. There were no significant associations between drinking alcohol and development of colorectal adenoma.

A total of 426 subjects (12.29%) had diabetes and 405 of these subjects (11.7%) had type-2 diabetes. Type-2 diabetes was associated with an increased risk of colorectal adenoma (Odds' ratio 1.35, 95% confidence interval 1.08-1.70, $p = 0.009$). Type-2 diabetes status was a significant predictor of the total no of colorectal adenomas detected in subjects during colonoscopies after adjusting for age, gender, smoking status and alcohol drinking. ($\beta = 0.167$, SE $\beta = 0.044$, $p < 0.001$)

Table 2 shows the relationship between different characteristics of adenoma and type-2 diabetes. The polyp detection rate was 37.1 % overall while it was significantly higher in subjects with type-2 diabetes 41.5% ($p= 0.02$). The overall adenoma detection rate **(ADR)** was 24.6%

and was significantly higher in subjects with type 2 diabetes 29.3% than non diabetic subjects 23.9% (p = 0.009). In addition subjects with type-2 diabetes had a significantly higher ADR in the proximal colon than the non-diabetic subjects, 19.72% versus 14.64% (p = 0.005). There was not a significant difference in the sessile serrated polyp detection rate **(SSPDR)** among those with type-2 diabetes and non-diabetic subjects. The total number of polyps and adenomas per subjects was significantly higher in subjects with type 2 diabetes compared to the non diabetic subjects (p <0.001).

Table 2: Differences of ADR among different demographic characteristic.

Characteristic	Non diabetic	Diabetic	*P* value
Male	30.01	31.28	0.708
Female	18.04	27.91	0.001*
Current Smoker	27.96	35.48	0.379
Formal Smoker	24.25	31.75	0.023 *
Never smoker	21.52	26.14	0.161
Alcohol Drinker	23.21	30.12	0.047*
Non alcohol drinker	22.01	28.94	0.022*

* p value <0.05 which suggest statistically significant difference.

As shown in Table 3, we also found statistically significant higher adenoma detection rates among female subjects with diabetes compared to non diabetic subjects. The subjects with type-2 diabetes who were female, former smokers (all smoking status?) both alcohol drinkers and non drinkers had significantly higher adenoma detection rates compared to those without diabetes. The type-2 diabeties status was a significant predictor of the total number of colorectal adenomas detected even after adjusting for age, gender, smoking status and alcohol drinking. Out of 426 subjects with diabetes, 21 subjects had type-1 diabetes and 405 subjects had type -2 diabetes. We did not find a significant difference in the development of colorectal adenoma detection rate among type-1 and type-2 diabetic subjects (23.81 vs. 29.88, p=0.55) albeit that the very small number of people in this study with type 1 diabetes makes this comparison weaker (Figures 1&2).

Table 3: Detection rate among diabetic and non diabetic subjects.

Factor	All Subjects (n=3465)	Non Diabetic (n=3038)	Diabetic (n=426)	*p*
1. PDR	37.1	36.5	41.5	<0.05
2. ADR	24.6	23.9	29.3	<0.05
a. Proximal ADR	15.3	14.64	19.72	0.006 < 0.05
b. Distal ADR	12.8	12.44	15.73	0.057
3. SSPDR	2.3	2.24	3.05	0.298
a. Proximal SSPDR	1.2	1.12	1.64	0.349
b. Distal SSPDR	1.2	1.15	1.64	0.385
4. No. of Polyps/Patient	0.70	0.67	0.91	<0.001
5. No of Adenoma /Patient	0.38	0.36	0.55	<0.001
a. Proximal Adenomas	0.22	0.20	0.32	<0.001
b. Distal Adenomas	0.17	0.15	0.22	0.008 < 0.05
6. No. of SSPs/Patient	0.030	0.029	0.042	0.278
a. Proximal SSP	0.013	0.012	0.018	0.308
b. Distal SSP	0.017	0.016	0.023	0.463

* p value <0.05 which suggest statistically significant difference. p values corresponds to paired t-tests (Diabetic and non diabetic subjects). PDR-Polyps detection rate, ADR- Adenoma detection rate, SSPDR- Sessile serrated polyps detection rate, SSP-Sessile serrated polyp.

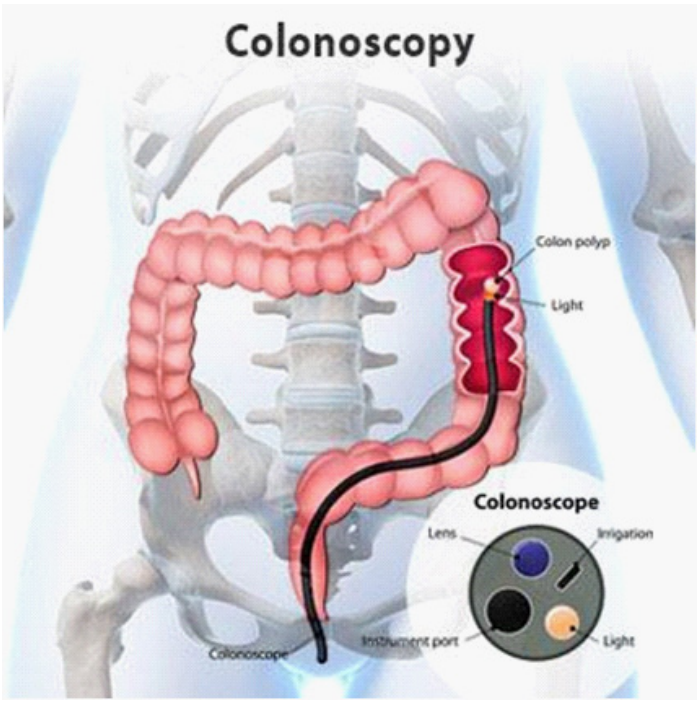

Figure 1: Colonoscopy.

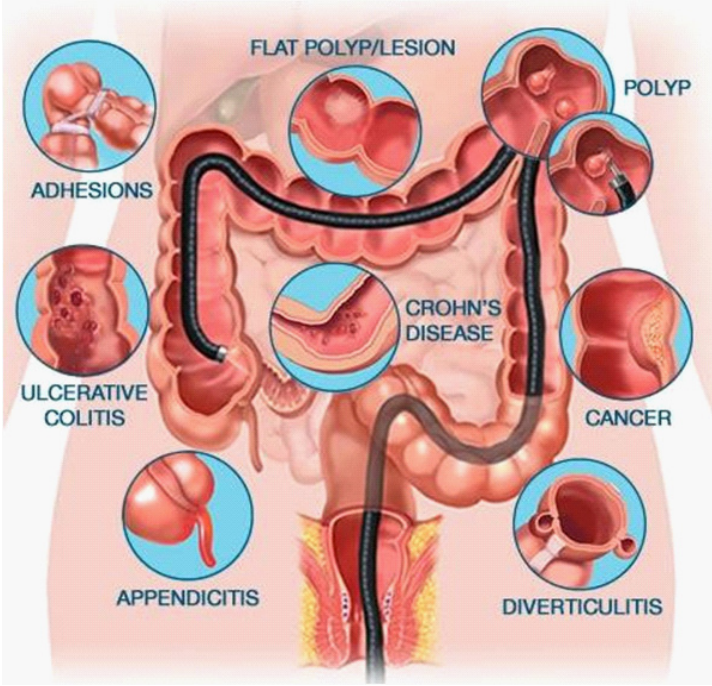

Figure 2: Chron's Disease.

DISCUSSION

Our study provided results that are consistent with previous studies which show an association between type 2 diabetes and colorectal adenoma[11,4,12]. More specifically in this study, subjects with type 2 diabetes had significantly higher rates of adenoma detection in the proximal colon. These findings are consistent with a previous study in Japan [12]. Sessile serrated polyps are primarily found in the proximal colon but we did not identify a difference between those with diabetes and non-diabetic subjects. A recent study has found a statistically significant increase in development of colorectal cancer from 18% to 32% among women with type 2 diabetes but there was no difference noticed among men [4,13]. We also found significant higher adenoma detection rate from 18.04 to 28.43 among women with type-2 diabetes compared to those without diabetes but this difference was not seen among male subjects. The rates of diabetes rate in this study (12.3%) were higher than national rates (8.3%) but likely reflect the impact of age on this cohort. This study only included subjects aged 50 years or higher. It is well known that type 2 diabetes rates increase with age. The U.S. Multi Society Task force on colon cancer published guidelines that suggest that among healthy asymptomatic patients older than 50 years undergoing screening colonoscopy, adenoma should be detected in ≥ 25% of the men and ≥ 15% women [14]. In this study the adenoma detection rate was 31.34% and 28.43% in men and women with type 2 diabetes respectively. Our overall 24.6% ADR was comparable to a more recent study which reported 28.8% and 25.5% among two different hospitals [15] (Table 4).

Table 4: Summary of Hierarchical Regression Analysis for predicting total no of colorectal adenoma. Linear regression analysis.

Variables	B(Entry)	B(Final)	SE B	Partial r	ΔF	ΔR²
Step-1					18.62*	0.005*
Diabetes$	0.188*	0.167*	0.044	0.073		
Step-2						
Age	0.007*	0.006*	0.002	0.075	34.67*	0.020*
Gender[a]	0.204*	0.185*	0.028	0.121		
Step-3					6.51*	0.009*
Current smoker[b]	0.110	0.110	0.101	0.019		
Former smoker[c]	0.004	0.004	0.093	0.001		
Never smoker[d]	-0.041	-0.041	0.092	-0.007		
Alcohol drinker[e]	-0.244#	-0.244#	0.073	-0.057		
Non alcohol drinker[f]	-0.228#	-0.228#	0.074	-0.053		

*p < 0.001, #p < 0.05

$ Diabetes was coded as 1 = Non diabetic subjects, 2= Diabetic subjects

a Gender was coded 1= Male, 0=Female,

b Current smoker coded 1= current smoker, other =0

c Former smoker coded 1 = Former smoker , other =0

d Never smoker coded 1 = Never smoker, Other= 0

e Alcohol Drinker 1= Alcohol drinker, Other = 0

f Non alcohol drinker 1 = non alcohol drinker, 0 = others

B(Entry) are the unstandardized regression coefficients from the first model in which the predictor was entered.

B(Final) are the unstandardized regression coefficients from the final model, i.e., the model that contained all of the predictors.

There are many theories which could explain the increased risk of colorectal adenoma or cancer in people with diabetes. One theory proposes that insulin like growth factor **(IGF-1)** and hyperinsulinemia contribute to the proliferation of colon epithelial cells and colon carcinoma cells, leading to colorectal cancer. (Berster & Goke 2008) In type-2 diabetic patients, hyperinsulinemia is present early in the disease in response to peripheral resistance to insulin [5,16]. Another theory suggests that a decrease in glucagon like peptide-1 **(GLP-1)** in patients with type 2 diabetes causes an increase in the expression of proto-oncogenes, such as c-Myc, which results in the proliferation of cells in colon and development of colorectal cancer [17]. Other co-morbidity

factors such as obesity, sedentary lifestyle and metabolic syndrome are also commonly seen among the both diabetic and colorectal cancer subjects [3]. These factors may explain part of the association between diabetes and colorectal cancer.

There are several limitations in this study. Due to the cross sectional retrospective study design we cannot make causal relationships between associations seen in our study. We were not able to determine the duration of diabetes in the study population. If the insulin resistance/ growth factor levels contribute to cancer neo genesis, then the duration of diabetes and even pre-diabetes could be critical. Further, the data we collected on met form in use was retrospective and the use was uncontrolled. In addition, we do not have the history of how long people were at each dose of met form in and a full history of other medications that could potentially affect the overall risk of colonic adenoma. Finally even though all of these colonoscopies were declared as screening colonoscopies we could not confirm that other contributing factors were or were not present. Despite these limitations, the findings of this study support an association between diabetes and colonic adenomas.

CONCLUSION

This study confirms the positive association between the risk of colorectal cancer and diabetes mellitus in this large retrospective study. It also supports the beneficial effect of met form in reducing the risk of developing colorectal adenoma. The average duration of met form in taken by the patient was 3.91 years. Prospective controlled studies should be completed to better explain these associations.

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