Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2010 December ; 19(12): 3027–3036. doi: 10.1158/1055-9965.EPI-10-0486.

Serial Glycosylated Hemoglobin Levels and Risk of Colorectal Neoplasia among Patients with Type 2 Diabetes Mellitus

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Abstract

Background—Hyperglycemia may increase the risk of colorectal neoplasia by serving as an energy source for neoplastic growth. We sought to determine whether glycemic control measured by serial hemoglobin A1C (HbA1c) was associated with the risk of colorectal adenoma.

Methods—Among a cohort of patients with type 2 diabetes mellitus who received healthcare within the Kaiser Permanente Northern California from 1994 to 2005, we conducted 2 case-control analyses. Cases had at least one colorectal adenoma identified at either colonoscopy (analysis-1) or sigmoidoscopy (analysis-2). Controls had no colorectal neoplasia identified at the corresponding endoscopic examination. Serial HbA1c levels between the cases and the controls were compared using a longitudinal model.

Results—Case-control analysis 1 included 4248 patients, of whom 1296 (31%) had at least one adenoma. The adjusted mean HbA1c levels among those without any adenomas was 8.20% versus 8.26% among those with at least 1 adenoma, a difference of 0.06% (95% CI: -0.02% to 0.14%, p=0.16). Case-control analysis 2 included 9,813 patients, of whom 951 (10%) had at least one distal adenoma. The adjusted mean HbA1c levels among those without any distal adenomas was 8.32% versus 8.37% among those with at least 1 distal adenoma, a difference of 0.05% (95% CI: -0.04% to 0.14%, p=0.25). The results were similar for advanced adenomas.

Conclusions—Glycemic control was not associated with the risk of colorectal adenoma among diabetics.

Impact—These results would suggest that glycemic control is unlikely to confound the reported association between diabetes medications and the risk of colorectal cancer.

Keywords

Colorectal adenoma; diabetes mellitus

Introduction

Colorectal cancer (CRC) develops in over 145,000 people in the United States annually.(1) Type 2 diabetes mellitus (DM), a metabolic condition characterized by insulin resistance, is

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Disclosure: None of the authors has any potential conflicts of interest that are relevant to the current manuscript.

associated with an increase in the risk of CRC.(2) One of the main mechanisms underlying this association is thought to be prolonged endogenous hyperinsulinemia.(3) Hyperglycemia also may influence CRC risk among type 2 DM patients by acting as a direct energy source and fueling increased proliferative activities in colorectal epithelium. These proliferation activities may by induced by growth factors such as insulin-like growth factor-I (IGF-I). This theory is consistent with the observation in animal models in which dietary carbohydrates promoted the growth of aberrant crypt foci.(4-6)

The primary treatment objective in type 2 DM is to achieve optimized glucose control on a long-term basis in order to prevent microvascular complications. If a clinically important association between levels of glycemic control and the risk of CRC is revealed, it would provide yet another motivating factor for patients with DM and their physicians to strive for strict glucose control. It would also influence the intensity of CRC screening efforts in patients with poor glucose control.

Existing epidemiological data linking measured average glucose level (e.g., hemoglobin A1c [HbA1c] levels) with adenoma or CRC risk in humans are conflicting.(7-13) However, none of these studies examined the association within a type 2 DM population. More importantly, none of these studies analyzed longitudinal data to capture the effect of long-term glycemic control. In the current study, we used data from the Kaiser Permanente of Northern California (KPNC) to examine whether the level of long-term glycemic control as measured by serial hemoglobin A1c (HbA1c) levels is associated with the risk of colorectal adenoma. HbA1c is a minor component of hemoglobin to which glucose is bound. HbA1c also is sometimes referred to as glycosylated hemoglobin or glycohemoglobin.

Methods

We conducted two case-control studies nested within a cohort of patients with DM who underwent large bowel endoscopies in the KPNC, one to examine neoplasia in the entire colon and another to focus primarily on distal adenomas. These analyses were part of a study that aims to examine the association between use of diabetes medications and the risk of colorectal polyp in the KPNC population.(14)

Data source

Approximately 3.2 million participants, representing one quarter of the population in the Northern California, receive comprehensive healthcare services through KPNC, a pre-paid healthcare system. For the entire study period of the current study (January 1, 1995 to December 31, 2005), medical and prescription information was systematically recorded in electronic databases at KPNC. The electronic databases also contain complete records on laboratory test results and endoscopic procedures. The pharmacy database includes information on each outpatient prescription dispensed at a KPNC pharmacy. KPNC launched a colon cancer screening program in 1994. However, flexible sigmoidoscopy was the primary screening tool and screening colonoscopy was not encouraged for average-risk patients.

Source cohort

From 1994 to 1996, a survey of patients with a possible diagnosis of DM was conducted in KPNC. These patients were identified from pharmacy data (prescriptions for diabetic medications), HbA1c level ≥6.7%, and outpatient, emergency room, and hospitalization records listing a diagnosis of DM. As of January 1, 1996, the identification method was estimated to be 90% sensitive.(15) From approximately 85,000 patients with type 1 or type 2 diabetes identified between 1994 and 1996, 62,465 completed the survey questionnaire and

were confirmed as having type 2 DM. For this study, patients with a history of inflammatory bowel disease, familial adenomatous polyposis syndrome, or hereditary non-polyposis colon cancer syndrome (n= 237) were excluded. Of the remaining 62, 228 patients, 14,086 underwent at least 1 colonoscopy or flexible sigmoidoscopy between January 1, 1999 and December 31, 2005 and comprise the source study cohort.

Depending on the type of large bowel endoscopies performed, a different subgroup of the source study cohort was used in each of the two case-control studies. Detailed description of the construction of the eligible source cohort for each of the case-control studies was reported previously.(14) Briefly, to be included in the first case-control study, patients were required to have undergone at least one colonoscopy between January 1, 1999 and December 31, 2005 (the first colonoscopy being defined as the index endoscopy), to have been at least 50 years old at the time of the index colonoscopy and to have continuous pharmacy benefits from KPNC between January 1, 1997 and the date of the index colonoscopy (n=4248). The second case-control study used the same inclusion criteria, except that the index endoscopy was a sigmoidoscopy (n=9813).

Selection of cases and controls

In the first case-control analysis, cases were defined as patients with one or more adenoma on the index colonoscopy or on a follow-up large bowel endoscopy within 6 months of the index colonoscopy.

In the second case-control analysis, cases were defined as patients with one or more adenomatous lesion in the distal colon (i.e., identified at sigmoidoscopy or if detected at a follow-up colonoscopy performed within 6 months of the index flexible sigmoidoscopy, located in the rectum or sigmoid colon or located in the distal 40cm if no anatomic segment was noted).

Control subjects were defined as patients without adenomatous lesions on the index endoscopy using the same anatomic criteria for the two analyses.

All pathology reports were manually reviewed by trained abstractors to determine the presence of adenomatous lesions. Agreement among the abstractors with regard to the presence or absence of adenoma was nearly perfect.(14)

Measurements of HbA1C

The primary exposure of interest was the mean HbA1c levels (%) within each yearly interval prior to the index colonoscopy. If a subject had more than 1 measurement during the yearly interval we used the arithmetic mean in primary analyses, and the maximum in secondary analyses. The American Diabetes Association guideline advocates that the glycosylated hemoglobin test be performed at least two times a year in patients with diabetes who are meeting treatment goals and quarterly in patients with diabetes whose therapy has changed or who are not meeting glycemic goals.

Potential confounding variables

We examined multiple potential confounders that may influence the risk of colon neoplasia and/or degree of glycemic control. Data on potential confounders were extracted from the diabetes survey (diabetes duration, body mass index [BMI], and race) and the KPNC electronic databases. These databases included registration files (age, sex, and location of residence), pharmacy data (acid suppression medications, statins, and nonsteroidal anti-inflammatory drugs [NSAIDs]), and procedure data (prior lower endoscopy) between January 1, 1995 and January 1, 1999. Household income was estimated based on the median

income of the census block of residency. For concomitant medications such as acid suppression medications, aspirin and NSAIDs, we required at least one year of cumulative exposure and use within the year preceding the index endoscopy to be considered exposed.

We included a variable for the most recent prior lower endoscopy during the period from January 1, 1995 to the index endoscopy to control for prior screening. We categorized this variable into five levels: no prior lower endoscopy, prior colonoscopy (with or without sigmoidoscopy) in the preceding 3 years, prior sigmoidoscopy without colonoscopy in the preceding 3 years, prior colonoscopy (with or without sigmoidoscopy) more than 3 years prior to the index endoscopy, and prior sigmoidoscopy without colonoscopy more than 3 years prior to the index endoscopy.

Statistical analyses

Longitudinal regression analysis was carried out using a mixed effects model with restricted maximum likelihood estimation of variance parameters. The mean HbA1c levels between the case and control groups were compared using this model adjusting for potential confounders listed in Table 1. We included time since the start of follow-up as a variable, as well as an interaction term that was constructed as the product of case-control group status and time. The estimates for the group-by-time interaction term did not differ significantly from zero (0.0007, p=0.46 in case-control study 1; -0.0065, p=0.56 in case-control study 2), indicating that the difference between cases and controls with respect to HbA1c did not depend on time. Therefore, we did not include the interaction term in the final longitudinal model.

Secondary analyses were performed defining case subjects as having advanced adenomas or early adenomas. We defined advanced adenoma according to the histology and did not include the polyp size since we did not have access to endoscopy reports. Advanced adenomas were defined as any adenoma with villous feature, high-grade dysplasia or invasive cancer.

The estimates for the group-by-time interaction term did not differ significantly from zero (0.0007, p=0.46 in case-control study 1; -0.0065, p=0.56 in case-control study 2), indicating that the difference between cases and controls with respect to HbA1c did not depend on time. Therefore, we did not include the interaction term in the final longitudinal model. We also explored including time as both a linear and quadratic term in the mixed effects model. Because this produced similar results as in the primary model for the association of adenoma status and HbA1c level, these data are not shown.

We also performed separate logistic regressions with HbA1c quartiles as exposure for each of the two-year intervals during the period from the start of follow-up for the source cohort to the index endoscopy (i.e., prior year 1-2, 3-4, 5-6, 7-8, 9-10). The HbA1c quartiles were based on the distribution of HbA1c levels among the no adenoma controls for each of the two-year interval during follow-back period. In this analysis, the odds ratios (ORs) compared the risk for quartiles 2, 3, 4, or missing relative to the lowest quartile. In addition to all the covariates adjusted in the longitudinal model, we also adjusted for year of endoscopy in the multivariable logistic regression model.

Results

As described previously,(14) cases and controls were relatively similar in terms of all baseline characteristics and across the two case-control studies, except that the cases were less likely to be female or regular users of NSAIDs over a long duration of time (Table 1).

Case-control study 1 – Adenoma in any region of the colon

During the study period, 4248 patients underwent at least one colonoscopy, of whom 1296 (31%) had at least one adenoma. The mean and median duration of follow-up prior to index colonoscopy in this cohort were 6.98 and 6.74 years, respectively, with an inter-quartile range of 5.24 to 8.60 years. Twenty-four patients in the control group and 13 patients in the case group (i.e., 0.8% of the total cohort) did not have any HbA1c measures during the follow-up before index colonoscopy and were effectively excluded in subsequent analysis involving HbA1c. Among the remaining >99% of the study cohort, >96% had at least one HbA1c measures in at least 2 separate prior yearly follow-up intervals; 82% of the controls and 79% of the cases had at least one HbA1c measure in at least 4 separate prior yearly follow-up intervals. The mean frequency of HbA1c measures per yearly follow-up interval was 1.5 with a standard deviation of 0.7.

The means of the yearly average HbA1c level in the cases and controls were comparable when analyzed by yearly intervals before index colonoscopy (Table 2). Furthermore, the means of yearly average HbA1c level continuously decreased at a similar rate in both groups from the beginning of the follow-up for the entire source cohort to the index colonoscopy, indicating that glucose control was improving as patients were followed in the KPNC (Table 2). We observed a similar pattern when we replaced mean of yearly average HbA1c levels by mean of yearly maximum HbA1c levels, or when we restricted the case group to those with advanced adenomas (data not shown).

In the longitudinal analysis of yearly within-person average HbA1c, after adjusting for sex, age, ethnicity and BMI, there was no statistically significant difference in the mean HbA1c levels over time between those with and without any adenomas. The adjusted mean HbA1c levels among those without adenomas was 8.27% versus 8.34% among those with at least one adenoma, yielding a non-statistically significant overall difference of only 0.075% (95% CI: -0.004% to 0.15%, p=0.07). After further adjustment for income status, duration of diabetes, NSAID use, aspirin use, statin use and use of acid suppressive medications, the adjusted mean HbA1c levels among those without any adenomas was 8.20% versus 8.26% among those with at least 1 adenoma, yielding an even smaller and still non-statistically significant overall difference of 0.06% (95% CI: -0.02% to 0.14%, p=0.14) (Table 3). The results were similar when we restricted the cases to those with advanced adenomas. In the fully adjusted longitudinal analysis, the adjusted mean HbA1c levels among the controls was 8.20% versus 8.28% among those with at least 1 advanced adenoma, giving a non-statistically significant difference of 0.07% (95% CI: -0.04% to 0.19%, p=0.24).

Similar to the longitudinal analysis, there was no association between levels of HbA1c in quartiles and the risk of any adenoma or advanced adenoma within each of the consecutive two-year intervals in multivariable logistic regression analysis (Table 4a).

Case-control study 2 – Adenoma in the distal colon

During the study period, 9813 patients underwent at least one lower endoscopy, of whom 951 (10%) had at least one distal adenoma. The mean and median duration of follow-up prior to index colonoscopy in this cohort were 6.64 and 6.24 years, respectively, with an inter-quartile range of 4.96 to 8.10 years. One hundred and six patients in the control group and 15 patients in the case group (i.e., 1.2% of the total cohort) did not have any HbA1c measures during the follow-up before index colonoscopy and were effectively excluded in subsequent analysis involving HbA1c. Among the remaining 99% of the study cohort, 96.5% had at least HbA1c measures in at least 2 separate prior yearly follow-up intervals; 77% of the controls and 75% of the cases had HbA1c measures in at least 4 separate prior

yearly follow-up intervals. The mean frequency of HbA1c measures per yearly follow-up interval was 1.5 with a standard deviation of 0.7.

The mean of average HbA1c levels across the cases and controls exhibited a similar trend as that observed in case-control study 1, except that the extent of improvement in mean yearly average HbA1c levels over the duration of follow-up was somewhat smaller in case-control study 2 (Table 2). Similar to study 1, HbA1c levels remained comparable between the cases and the controls when we replaced mean of yearly average HbA1c levels by mean of yearly maximum HbA1c levels, or when we restricted the case group to those with advanced adenomas (data not shown).

In the longitudinal analysis accounting for yearly average HbA1c levels in each patient, after adjusting for sex, age, ethnicity and BMI, there was no statistically significant difference in the mean HbA1c levels over time between those with and without any adenomas. The adjusted mean HbA1c levels among those without adenomas was 8.38% versus 8.44% among those with at least one adenoma, yielding a non-statistically significant overall difference of only 0.057% (95% CI: -0.003% to 0.15%, p=0.21). After further adjustment for income status, duration of diabetes, NSAID use, aspirin use, statin use and use of acid suppressive medications, the adjusted mean HbA1c levels among those without any adenomas was 8.32% versus 8.37% among those with at least 1 adenoma, yielding an even smaller and still non-statistically significant overall difference of 0.05% (95% CI: -0.04% to 0.14%, p=0.25) (Table 3). The results were similar when we restricted the cases to those with advanced adenomas. In the fully adjusted longitudinal analysis, the adjusted mean HbA1c levels among the controls was 8.32% versus 8.42% among those with at least 1 advanced adenoma, giving a non-statistically significant difference of 0.09% (95% CI: -0.06% to 0.25%, p=0.24).

Similar to the longitudinal analysis, there was no statistically significant association between levels of HbA1c in quartiles and the risk of any adenoma or advanced adenoma within consecutive two-year intervals in multivariable logistic regression analysis, except for very modest increases in any adenoma risk of borderline statistical significance associated with missing HbA1c category in prior year 1-2 and quartile 3 in prior year 5-6, compared to their respective quartile 1 categories (Table 4b).

Discussion

In this study, the mean yearly level of HbA1c measured during up to 10 years of prior follow-up was not significantly different between DM patients with any adenoma compared to patients without any adenoma. Furthermore, compared to patients with yearly average HbA1c levels in the lowest quartile, patients with HbA1c in higher quartiles did not have increased risks for adenoma. This is true regardless of the adenoma grade (i.e., advanced adenoma versus any adenoma) or location (i.e., entire colon found during colonoscopy versus distal colon detected on flexible sigmoidoscopy).

Several previous studies have examined the association between glucose levels or HbA1c levels and the risk of colorectal neoplasia. None of these studies was conducted in a DM-only population. Schoen et al. conducted a cohort study among 5849 participants of the Cardiovascular Health Study Cohort who had fasting and 2-hour post-oral glucose challenge glucose levels measured at baseline. They found that individuals in the highest quartile of fasting glucose had a nearly twofold increased risk of CRC (relative risk [RR] 1.8; 95% CI: 1.0-3.1). Plasma glucose levels 2 hours after oral glucose challenge also exhibited statistically significant associations with CRC (RR 2.4; 95% CI:1.2-4. 7).(7) Consistent with these data, Khaw et al. reported from the European Prospective Investigation into Cancer-

Norfolk cohort that the RR (95% CI) of incident CRC per 1% absolute increase in baseline HbA1c was 1.34 (1.12-1.59; $p < 0.001$).(8) In a later study including the entire EPIC cohort, a positive association between HbA1c and colorectal cancer was confirmed, but the effect was much less strong (OR, 1.10; 95% CI, 1.01-1.19 for a 10% increase in HbA1c).(16)

However, other studies failed to observe a clear association between glucose levels and the risk of colorectal neoplasia. Platz et al. conducted a case-control study among a small sample of the Nurses' Health Cohort who had HbA1c measured once before the index date with up to 5 years of follow-up. (9) They found that HbA1c level did not significantly differ between CRC cases (median 5.5%) and controls (5.5%, $p = 0.5$), although a small difference between adenoma cases (5.6%) and controls (5.5%, $p = 0.06$) was noted. Compared to the lowest tertile of HbA1c (median 5.2%), women in the middle and upper (median 5.8%) tertiles were not at an increased risk for CRC. In a secondary analysis, a modestly elevated risk of distal colorectal adenoma in the upper versus lower tertile could not be excluded (OR 1.4, 95% CI: 0.9-2.3).(9) A further analysis of the same cohort extending the follow-up duration to 10 years also found no clear association between glycosylated hemoglobin and risk for CRC.(12) Yamada et al performed a case-control study among a group of Japanese undergoing a health checkup. No significant association between colorectal carcinoma in situ and fasting plasma glucose level was observed. However, a modest increase of colorectal carcinoma in situ risk was observed in the highest category (> or =116 mg/dl) of fasting plasma glucose levels.(10) In another case-control study among participants in a community-based cohort in Maryland, Saydah et al. observed a modest but non-statistically significant increase in the risk of CRC among those in the highest fourth of HbA1c compared to those at the lowest fourth (OR 1.57, 95% CI: 0.9-2.6).(11) Lin et al. analyzed 27,110 participants of the Women's Health Study and found no increased risk of CRC over 10 years of follow-up among those with higher baseline HbA1c levels.(13) Furthermore, there are meta-analyses of data from randomized controlled trials on glycemic control and cancer risk. While numbers are not sufficient enough to analyze by cancer type, a similar picture of null association emerges.(17,18)

Our study further elucidates the association between glycemic status and risk of colorectal neoplasia in several respects. First, our analysis was conducted among a cohort of DM patients with a wide distribution of HbA1c levels. In contrast, all of the prior studies were conducted either in the general population or a non-DM population where the HbA1c levels were generally within a relatively narrow and low range. Based on the hypothesized mechanism that hyperglycemia might be involved in colorectal carcinogenesis by providing the energy substrate to support increased proliferative activity induced by other factor (e.g., IGF-I), it may be more biologically relevant to examine the effect of HbA1c in moderate to high ranges and in a setting of DM. Second, all of the previous studies analyzed a one-time measure of either glucose level or HbA1c level as the exposure or predictor variable. It is doubtful that a single baseline measurement could adequately reflect the glycemic load over the long duration of colorectal carcinogenesis. In contrast, we analyzed serial HbA1c measurements using a longitudinal model. Indeed, we observed marked changes in the level of average HbA1c in our cohort over the course of the follow-up, suggesting that performing longitudinal analysis using serial HbA1c measurements was critical in this context. Nevertheless, we did no find any association between HbA1c and the risk of colorectal neoplasia.

There has been a growing interest in evaluating the effect of diabetes treatment on the risk of colon cancer and cancer in general because diabetes medications can theoretically alter cancer risk by affecting hyperinsulinemia, a postulated important promoter of carcinogenesis.(19) Furthermore, metformin may have a direct anti-proliferative effect.(20) However, use of these medications is associated with the status of glucose control.

Specifically, poor glucose control may be the indication for initiating diabetes medications, while their use may improve glucose control. In order to elucidate the specific mechanisms underlying the reported association between diabetes medications and cancer risk, it is important to determine whether glucose control is a confounder and/or an intermediate, which would require complex statistical modeling to account for these effects. Our results would suggest that glucose control is neither a confounder nor an intermediate in this context because it was not associated with colorectal neoplasia risk. Furthermore, these results indirectly support the notion that the previously reported association between diabetic medications and colorectal cancer risk is likely due to mechanisms independent of level of glucose control.

Several potential limitations of the study are worth noting. First, we did not have sufficient incident CRC cases to meaningfully examine the effect of hyperglycemia on this endpoint. However, we believe the surrogate endpoint of adenoma or advanced adenoma has clinical relevance because the objective of the current CRC prevention program is to remove colorectal precursor lesions before they progress to invasive cancer. Thus, data on the risk of adenoma can inform screening policies. Second, given the long duration expected for colorectal adenoma growth, it is possible that some of the HbA1c measurements close to the index endoscopy would not have an effect on initial adenoma formation. However, hypothesized as an energy source for increased proliferation, hyperglycemia is more likely to have an effect on adenoma growth, progression or regression rather than adenoma induction. Therefore, inclusion of these later measurements makes biological sense.

One might question whether inclusion of endoscopies for both evaluation of symptoms and screening may have biased the results. However, symptoms are not strongly correlated with the prevalence of colonic neoplasia(21,22). While nearly half of the sigmoidoscopies were likely for screening, very few of the colonoscopies were for screening in this health plan during the study period. However, the results of our primary analysis were similar for the cohort who underwent colonoscopy and the cohort who underwent sigmoidoscopy. Similarly, the HbA1c levels were similar between these groups. Furthermore, any potential bias is minimized in the current study by only including people who actually had the procedure. The issue of screening vs. diagnostic procedures is more relevant when discussing the effectiveness of the screening tests at preventing disease or mortality, not when measuring disease risk factor. Thus, it is unlikely that the inclusion of patients undergoing lower endoscopy to evaluate symptoms has biased the results.

Based on recent data, there are complex non-linear relationships between HbA1c and mortality, weight, diabetes treatment.(23) It is possible that the relationship between HbA1c and colorectal neoplasia may be non-linear as well, but we did not see evidence of non-linearity across the range of mean yearly HbA1c levels during the follow-up (Table 2), nor via introduction of polynomial terms for time in the longitudinal model. In addition, we did not observe such a non-linear association in the secondary analysis by quartiles of HbA1c.

We chose not to include DM medications in the longitudinal model as potential confounders for several reasons. First, none of the DM medications was shown to be associated with CRC risk in the KPNC population,(14) making them unlikely confounders in the current study. Nevertheless, since insulin therapy was associated with the risk of CRC in a UK population,(19) we repeated our analyses after excluding patients who were ever exposed to insulin in KPNC. Similar to our primary analysis, this restriction analysis showed no significant difference in adjusted mean HbA1c levels between those with adenoma and those without adenoma (HbA1c difference from fully adjusted mixed model: 0.06% [95% CI: -0.04 to 0.16%] for any adenoma; 0.06% [95%CI: -0.06% to 0.16%] for distal adenoma). Therefore, confounding by DM medication is unlikely. Furthermore, DM medications may

be added or discontinued based on HbA1c levels in clinical practice, which would make them intermediates in the causal pathway between glycemic status and CRC risk. As such, their inclusion in the model would have biased the results towards the null.

Our objective was to evaluate whether serial HbA1c was associated with colorectal cancer risk within the range of levels expected among diabetics. Therefore, our results may not be generalizable to populations without diabetes. In addition, while our overall results do not support a positive association between serial HbA1c levels and the risk of colorectal cancer among type 2 diabetics, the confidence intervals of some of our point estimates were compatible with a modest positive association.

In conclusion, our data suggest that long-term glycemic control as measured by HbA1c is not associated with the risk of colorectal adenoma among patients with type 2 DM. Further studies are needed to confirm our findings, and the wide variations in HbA1c levels observed among type 2 DM patients over several years in our study indicate that it is essential for future studies to use longitudinal HbA1c measurement. If our results are confirmed, they would suggest that glycemic control is unlikely to confound the reported association between diabetes medications and the risk of colorectal cancer.

Acknowledgments

Grant Funding: This work was funded by National Institute of Health grant CA102599. The study sponsor played no role in the study design, in the collection, analysis, and interpretation of data.

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Table 1

Characteristics of TZD users and non-users.

	Study – 1 Adenoma anywhere in the colon		Study – 2 Distal Adenoma	
	Cases N=1296	**Controls N=2952**	**Cases N=951**	**Controls N=8862**
Female (%)	41	49	37	46
Age (median years, IQR)	71 (65-77)	71 (64-77)	67 (60-74)	66 (60-73)
Race (%)				
White	60	59	57	52
Black	14	12	12	16
Hispanic	12	12	12	13
Asian	10	11	14	14
Other	2	3	2	3
Missing	2	3	2	3
BMI (%)				
25 or less	17	17	16	17
>25 to 30	36	34	38	34
>30	36	38	36	37
Missing	10	11	10	12
Socioeconomic status (%)				
< median	49	47	42	45
≥ the median	49	50	55	52
Missing	3	3	2	3
Diabetes duration (%)				
Less than 5 years	26	30	34	33
5 to <10 years	25	23	25	24
10 or more years	39	40	32	35
Missing	10	8	9	9
Concomitant medications* (%)				
NSAID	12	17	11	15
Aspirin	2	2	1	1
Proton pump inhibitor	4	6	2	3
Statin	38	38	32	34
Most recent lower endoscopy during 1995-1998 (%)				
Colonoscopy ≤ 3 years prior**	5	5	1	1
Sigmoidoscopy ≤ 3 years prior**	5	5	1	3
Colonoscopy > 3 years prior**	19	19	3	3
Sigmoidoscopy >3 years prior**	19	22	11	16
None	53	49	84	78

	Study – 1 Adenoma anywhere in the colon		Study – 2 Distal Adenoma	
	Cases N=1296	**Controls N=2952**	**Cases N=951**	**Controls N=8862**
Lower endoscopy with polypectomy 1995-1998 (%)	18	16	5	4

* At least one year of cumulative use and use within 1 year of the index date

** Prior to index date

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Table 2

Mean and standard deviation (SD) of yearly average HbA1c levels by year prior to index large bowel endoscopy

	Case-Control Study 1			Case-Control Study 2		
	Any Adenoma	**Advanced Adenoma**	**No Adenoma**	**Any Adenoma**	**Advanced Adenoma**	**No Adenoma**
Prior Year 1						
n	1155	434	2669	853	257	7984
Mean (SD) %	7.64 (1.51)	7.60 (1.51)	7.55 (1.39)	7.89 (1.49)	7.84 (1.55)	7.91 (1.59)
Prior Year 2						
n	1079	394	2496	736	222	7098
Mean (SD) %	7.75 (1.60)	7.78 (1.67)	7.83 (1.60)	8.09 (1.68)	8.11 (1.79)	8.03 (1.69)
Prior Year 3						
n	1015	388	2363	706	213	6846
Mean (SD) %	7.94 (1.68)	7.96 (1.79)	7.98 (1.65)	8.08 (1.76)	8.06 (1.78)	8.13 (1.72)
Prior Year 4						
n	975	365	2269	680	208	6531
Mean (SD) %	8.18 (1.78)	8.09 (1.74)	8.09 (1.70)	8.24 (1.79)	8.13 (1.81)	8.22 (1.75)
Prior Year 5						
n	872	314	2059	593	185	5777
Mean (SD) %	8.19 (1.73)	8.11 (1.71)	8.21 (1.70)	8.29 (1.76)	8.28 (1.86)	8.27 (1.75)
Prior Year 6						
n	667	253	1602	407	118	4256
Mean (SD) %	8.12 (1.73)	8.09 (1.85)	8.24 (1.83)	8.32 (1.71)	8.17 (1.59)	8.24 (1.73)
Prior Year 7						
n	518	199	1184	315	97	3007
Mean (SD) %	8.27 (1.82)	8.30 (1.98)	8.27 (1.85)	8.44 (1.88)	8.37 (1.75)	8.34 (1.81)
Prior Year 8						
n	366	150	851	206	62	2086

	Case-Control Study 1			Case-Control Study 2		
	Any Adenoma	**Advanced Adenoma**	**No Adenoma**	**Any Adenoma**	**Advanced Adenoma**	**No Adenoma**
Mean (SD) %	8.32 (1.97)	8.37 (1.84)	8.41 (1.83)	8.34 (1.95)	8.35 (1.92)	8.28 (1.78)
Prior Year 9						
n	271	105	560	115	40	1391
Mean (SD) %	8.46 (1.78)	8.60 (1.80)	8.43 (1.83)	8.32 (1.91)	8.63 (1.93)	8.34 (1.74)
Prior Year 10						
n	150	61	302	67	18	840
Mean (SD) %	8.55 (1.82)	8.28 (1.68)	8.54 (1.75)	8.33 (1.83)	8.29 (2.03)	8.29 (1.67)

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Table 3

Longitudinal analysis comparing mean yearly average HbA1c levels among case groups with any adenoma or advanced adenoma versus controls without any adenoma.

	Study 1 – Adenoma anywhere in the colon			Study 2 – Distal Adenoma		
	No Adenoma	**Advanced Adenoma**	**Any Adenoma**	**No Adenoma**	**Advanced Adenoma**	**Any Adenoma**
N	2,952	478	1,296	8,862	289	951
Mean Estimate* (SE) (%)	8.20 (0.026)	8.28 (0.057)	8.26 (0.036)	8.32 (0.016)	8.42 (0.079)	8.37 (0.044)
Difference in mean estimates** (95% CI, p) (%)	Reference	0.07 (-0.04 to 0.19, p=0.24)	0.06 (-0.02 to 0.14, p=0.16)	Reference	0.09 (-0.06 to 0.25, p=0.24)	0.05 (-0.04 to 0.14, p=0.25)

SE = Standard error

* Least Squares Means adjusted for sex, age, ethnicity, BMI, income status, duration of diabetes, NSAID use, aspirin use, statin use and use of acid suppressive medications.

** Based on longitudinal analysis adjusted for sex, age, ethnicity, BMI, income status, duration of diabetes, NSAID use, aspirin use, statin use and use of acid suppressive medications.

Table 4a

Logistic regression analysis with HbA1c quartile as exposure in two-year intervals (Study 1 – Adenoma anywhere in colon)*

HbA1c Quartile	Prior Year 1-2		Prior Year 3-4		Prior Year 5-6		Prior Year 7-8		Prior Year 9-10	
	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)
3.40-6.90	Reference n=403	Reference n=148	Reference n=291	Reference n=110	Reference n=224	Reference n=86	Reference n=131	Reference n=57	Reference n=61	Reference n=24
6.91-7.78	1.0 (0.9-1.2) n=349	1.2 (0.9-1.6) n=141	1.1 (0.9-1.4) n=301	1.3 (0.9-1.7) n=126	1.0 (0.8-1.3) n=246	1.0 (0.7-1.5) n=97	1.2 (0.9-1.7) n=126	0.9 (0.6-1.5) n=40	0.9 (0.6-1.4) n=58	0.9 (0.5-1.8) n=24
7.79-8.90	1.0 (0.8-1.2) n=276	1.1 (0.8-1.5) n=102	1.0 (0.8-1.2) n=283	0.9 (0.6-1.3) n=96	0.8 (0.7-1.1) n=245	0.8 (0.6-1.2) n=93	1.0 (0.7-1.4) n=141	1.1 (0.7-1.7) n=61	1.0 (0.6-1.5) n=66	0.8 (0.4-1.5) n=20
8.91-17.9	1.1 (0.9-1.4) n=219	1.1 (0.7-1.6) n=71	1.2 (0.9-1.5) n=291	1.2 (0.8-1.7) n=103	1.0 (0.7-1.3) n=293	0.9 (0.6-1.3) n=95	1.0 (0.8-1.4) n=191	1.0 (0.6-1.6) n=74	1.1 (0.7-1.7) n=123	1.3 (0.7-2.4) n=55
Missing	0.9 (0.6-1.3) n=49	0.8 (0.4-1.4) n=16	1.3 (1.0-1.7)† n=130	1.2 (0.8-1.8) n=43	1.0 (0.8-1.3) n=288	1.1 (0.7-1.5) n=107	1.1 (0.8-1.5) n=707	1.0 (0.7-1.6) n=246	0.8 (0.5-1.1) n=988	0.9 (0.5-1.5) n=355

Table 4b. Logistic regression analysis with HbA1c quartile as exposure in two-year intervals (Study 2 - Distal Adenoma)*

HbA1c Quartile	Prior Year 1-2		Prior Year 3-4		Prior Year 5-6		Prior Year 7-8		Prior Year 9-10	
	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)	Any adenoma Adjusted OR** (95% CI)	Advanced adenoma Adjusted OR** (95% CI)
4.46-7.00	Reference n=248	Reference n=94	Reference n=224	Reference n=67	Reference n=156	Reference n=46	Reference n=86	Reference n=24	Reference n=35	Reference n=11
7.01-7.87	1.0 (0.8-1.3) n=238	0.6 (0.4-0.9)† n=59	1.0 (0.8-1.2) n=199	1.1 (0.7-1.6) n=62	1.1 (0.8-1.4) n=141	1.4 (0.9-2.1) n=51	1.0 (0.7-1.4) n=69	1.1 (0.6-2.0) n=22	0.9 (0.5-1.6) n=27	0.4 (0.1-1.3) n=4
7.88-9.10	1.0 (0.8-1.3) n=225	0.7 (0.5-1.1) n=63	0.9 (0.7-1.1) n=211	1.1 (0.7-1.6) n=66	1.3 (1.0-1.7)† n=212	1.3 (0.8-2.1) n=60	1.1 (0.7-1.5) n=90	1.1 (0.6-2.1) n=28	0.8 (0.5-1.3) n=38	1.1 (0.5-2.5) n=17
9.10-17.5	1.1 (0.9-1.4) n=185	0.9 (0.6-1.4) n=55	1.0 (0.8-1.3) n=211	1.1 (0.7-1.7) n=58	1.0 (0.8-1.4) n=175	1.1 (0.7-1.8) n=52	1.1 (0.8-1.6) n=114	1.3 (0.7-2.3) n=32	0.9 (0.6-1.6) n=40	1.1 (0.5-2.7) n=15
Missing	1.5 (1.1-2.1)† n=55	1.3 (0.7-2.2) n=18	1.0 (0.7-1.3) n=106	1.2 (0.8-1.9) n=36	1.2 (0.9-1.5) n=267	1.2 (0.8-1.9) n=80	0.9 (0.7-1.3) n=592	1.5 (0.9-2.6) n=183	1.1 (0.7-1.8) n=811	0.9 (0.4-1.9) n=242

* Patients without any adenoma as controls

** Adjusted for sex, age, ethnicity, BMI, income status, year of large bowel endoscopy, duration of diabetes, NSAID use, aspirin use, statin use and use of acid suppressive medications.

† $P<0.05$