Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Associations of Colonoscopy and Risk of Hypoglycemia in Patients with Type 2 Diabetes

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Purpose: Inpatients undergoing colonoscopy may be at increased risk of hypoglycemia. However, few high-quality studies have examined the relationship between hypoglycemia and colonoscopy in patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: A total of 1016 patients from a large tertiary hospital were enrolled in this retrospective study. We collected demographic information, laboratory indices, colonoscopy information and hypoglycemia information from the enrolled patients during hospitalization. Logistic regression analysis was adopted to estimate the adjusted odds ratios to determine the association between hypoglycemia and colonoscopy.

Results: Hypoglycemia occurred in 80 of 788 (10.1%) patients without colonoscopy exposure and 37 of 228 (16.2%) patients with colonoscopy exposure. 25 patients (67.6%) had hypoglycemic events from 3 hours to 68 hours after the end of colonoscopy. Adjusting for demographic and clinical covariates, the risk of hypoglycemia was 1.99 times higher in those who underwent colonoscopy than in those who did not (OR 1.99, 95% CI 1.25–3.19). The association was consistent in subgroups of females, the elderly, the overweight patients, patients with long duration of disease or patients with suboptimal glycemic control.

Conclusion: A strong association between colonoscopy and an increased risk of hypoglycemia is observed in patients with T2DM. When performing a colonoscopy for diabetics, the risk of hypoglycemia should be considered even within 68 hours after colonoscopy.

Keywords: hypoglycemia, colonoscopy, type 2 diabetes mellitus, retrospective study, fasting

Introduction

Hypoglycemia is a common complication in the clinical management of patients with diabetes. There is growing evidence that severe hypoglycemia is associated with impaired cognitive function, increased risk of cardiovascular events, and an estimated 50% to 600% risk of mortality.[1] Identifying the risk factors affecting hypoglycemia and reducing the incidence of hypoglycemia are key goals in the treatment of diabetic patients.[2]

Considering that type 2 diabetes mellitus (T2DM) is associated with an increased risk of colon cancer,[3–5] patients with T2DM reported higher demand for colonoscopy screening than the general population.[6] Dietary changes, prolonged fasting, laxatives-using, and changes in anti-hyperglycemic prescription regimens all increase the risk of hypoglycemia in diabetics undergoing colonoscopy. Previous studies have reported an incidence of 3.2–43.5% of hypoglycemia in children undergoing colonoscopy.[7,8] A randomized clinical trial of 150 diabetic patients showed that only 4 hypoglycemic events (2.7%) occurred in patients undergoing colonoscopy.[9] The previous three studies reported wide variation in the incidence of hypoglycemia and were limited by the relatively small sample sizes. Few large population-based data have been reported concerning the prevalence of hypoglycemia in diabetic patients undergoing colonoscopy. Most previous studies have focused on the glycemic status before colonoscopy,[7–9] but clinically observed hypoglycemia events frequently occur after colonoscopy. In addition, the occurrence of hypoglycemic events is self-reported or measured only once by a point-of-care blood test before colonoscopy, which is relatively less objective and comprehensive, suggesting that the occurrence of hypoglycemia may be underestimated.

Received: 29 December 2022
Accepted: 27 March 2023
Published: 29 March 2023

A single-center retrospective study was conducted to calculate the incidence rates of hypoglycemia in diabetic patients undergoing colonoscopy and evaluate the associations between colonoscopy and hypoglycemia. We hypothesized that colonoscopy would increase the risk of hypoglycemia in hospitalized patients with T2DM.

Materials and Methods

Data Sources

The investigation was conducted in the department of endocrinology in China from January 2021 to October 2022. Data were obtained from Hospital Information System which recorded all the patient data throughout hospitalization.

Ethical Considerations

The study was approved by the medical ethics committee in Shenzhen Traditional Chinese Medicine Hospital (approval number K2022-148-01). The hospital ethics committee has approved the waiver of informed consent because the medical records used in this study were obtained from previous clinical consultations. In order to protect the patients' personal privacy, identity-sensitive information such as the name, address, and phone number of the subjects were not collected for this research study. We have maintained the confidentiality of patient information as required by law.

Study Population

Patients (≥ 18 years old) diagnosed with T2DM in accordance with the International Classification of Diseases, 10th Revision (ICD-10: E11) were identified. A total of 1249 patients with T2DM were enrolled in the study, 1026 of whom were finally screened for the study. We established exclusion criteria with reference to previous studies.[10–12] The detailed screening process is illustrated in Figure 1.

Hypoglycemia

The primary study outcome was the occurrence of hypoglycemia ascertained by point-of-care blood testing in capillary blood and recorded in the hospital's blood glucose management system. Hypoglycemia was defined based on ICD-10: E16.2 (Blood glucose < 3.9 mmol/L [70 mg/dL]).

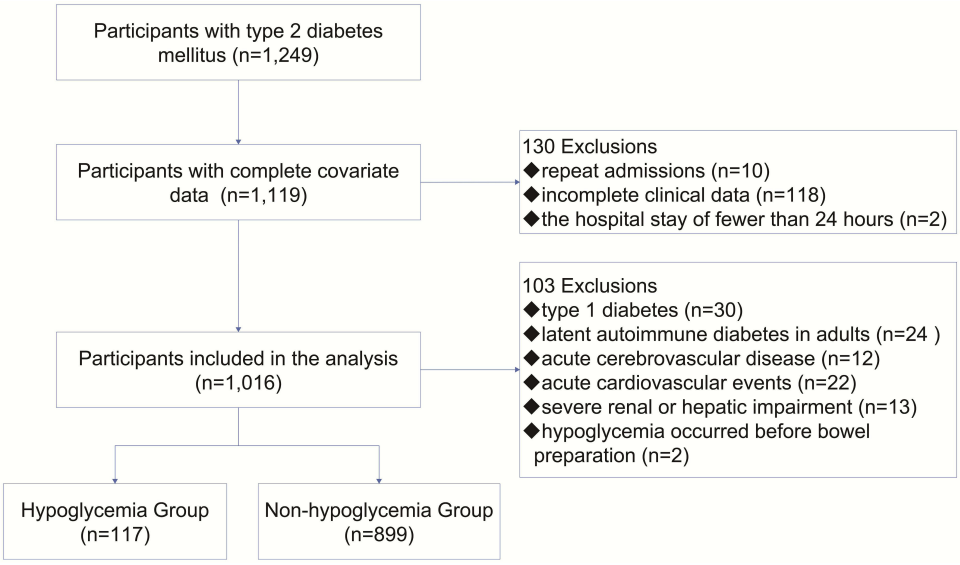

Figure 1 Study flow diagram.
Notes: Severe hepatic impairment (alanine aminotransferase, or aspartate aminotransferase; total bilirubin levels > 3.0 times over the upper limit of normal); severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2).

Colonoscopy and Covariate

Colonoscopy results were obtained from the Hospital Information System. The pathogenesis of hypoglycemia in diabetic patients is complex, along with numerous risk factors.[13] The covariates of our study were identified by searching the database (PubMed and Medline) and consulting experts,[14–16] covering age, gender, the length of hospital stay, diabetes duration, body mass index (BMI), chronic complications (diabetic retinopathy, diabetic peripheral neuropathy, diabetic peripheral vascular disease, diabetic nephropathy, and diabetic foot), other comorbidities (coronary atherosclerosis, hypertension, cerebrovascular disease, hyperlipidemia, and coronary heart disease), laboratory indicators (glycated hemoglobin, fasting plasma glucose [FPG], 2-hour plasma glucose [2h PG], fasting C-peptide [FCP], 2-hour C-peptide [2h CP], triglyceride [TG], total cholesterol [TC], HDL cholesterol [HDL-c], LDL cholesterol [LDL-c], blood urea nitrogen [BUN], serum creatinine, estimated glomerular filtration rate [e-GFR] and urine microalbumin-creatinine ratio), and antidiabetic medications (insulin, sulfonylurea, metformin, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, Sodium-glucose cotransporter protein-2 and α-glucosidase inhibitors). The duration of diabetes refers to the number of years from the time of the first diabetic diagnosis to the index date.

Statistical Analysis

SPSS 25.0 was used for statistical analysis, the person performing the statistical analysis was blinded to the hypothesis. Continuous variables were presented by mean ± SD, or by median (interquartile range) in the case of a skewed distribution. Categorical variables were expressed as proportions. We adopted χ^2 test, Student's *t*-test and the nonparametric Mann–Whitney *U*-test as appropriate, to examine the relationship between hypoglycemia and all the research variables. Binary logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI). Based on the relevant factors, subgroup analysis was performed to compare the correlation between hypoglycemia and colonoscopy. Statistical significance was defined as two-sided *p* values less than 0.05.

Results

A total of 1016 subjects were enrolled finally, of whom 117 with hypoglycemia and 899 without hypoglycemia were recorded by the hospital's blood glucose management system. As shown in Table 1, 603 of the subjects (59.4%) were male, with a median

Table 1 Baseline Characteristics of the Patients Included in the Study (n = 1016)

Variable	Hypoglycemia Group (n=117)	Non-Hypoglycemia Group (n=899)	*p* value
Gender, n (%)			NS
Female	56 (47.9)	357 (39.7)	
Male	61 (52.1)	542 (60.3)	
Age (years), mean ± SD	58.08 ± 13.84	57.29 ± 13.56	NS
Length of hospital stay (days), mean ± SD	11.46 ± 4.54	9.75 ± 4.12	<0.001
Duration of diabetes (years), mean ± SD	12.60 ± 9.10	10.03 ± 7.86	0.001
BMI (kg/m^2), mean ± SD	24.32 ± 3.68	24.64 ± 3.42	NS
Diabetic complications, n (%)			
Diabetic retinopathy	48 (41.0)	260 (28.9)	0.008
Diabetic peripheral neuropathy	86 (73.5)	542 (60.3)	0.006
Diabetic peripheral vascular disease	88 (75.2)	638 (71.0)	NS

(*Continued*)

Table 1 (Continued).

Variable	Hypoglycemia Group (n=117)	Non-Hypoglycemia Group (n=899)	*p* value
Diabetic nephropathy	25 (21.4)	113 (14.79)	0.010
Diabetic foot	4 (3.4)	12 (1.3)	NS
Comorbidities, n (%)			
Hypertension	51 (43.6)	394 (43.8)	NS
Cerebrovascular disease	16 (13.6)	165 (18.4)	NS
Hyperlipidemia	55 (47.0)	374 (41.6)	NS
Coronary heart disease	12 (10.3)	107 (11.9)	NS
Antidiabetic drugs, n (%)			
Insulin	86 (73.5)	526 (58.5)	0.002
Total insulin dose (U), mean ± SD	25 (0, 37)	20 (0, 30)	<0.001
Metformin	44 (37.6)	420 (46.7)	NS
Sulfonylureas	9 (7.6)	126 (14.0)	NS
α-Glucosidase inhibitors	12 (10.3)	73 (8.1)	NS
Thiazolidinediones	1 (0.8)	13 (1.4)	NS
DDP-4 inhibitors	46 (39.3)	391 (43.5)	NS
SGLT2	38 (32.5)	371 (41.3)	NS
Laboratory data			
HbA_{1c} (%)	9.13 ± 2.60	9.00 ± 2.38	NS
Fasting plasma glucose (mmol/L)	7.76 ± 4.00	8.70 ± 3.38	0.006
2-hour plasma glucose (mmol/L)	11.50 ± 5.09	13.03 ± 4.76	0.001
Fasting C-peptide (mmol/L)	1.74 ± 1.12	1.81 ± 1.13	<0.001
2-hour C-peptide (mmol/L)	3.23 ± 3.12	4.53 ± 3.17	<0.001
Triglyceride (mmol/L), *M* (P_{25}, P_{75})	1.44 (0.94, 2.04)	1.47 (1.03, 2.32)	NS
Total cholesterol (mmol/L), *M* (P_{25}, P_{75})	4.37 (3.68, 5.26)	4.41 (3.63, 5.22)	NS
HDL-C (mmol/L)	1.12 ± 0.31	1.06 ± 0.71	NS
LDL-C (mmol/L)	2.78 ± 1.07	2.69 ± 1.00	NS
eGFR (mL/min/1.73 m^2)	82.99 ± 26.46	89.28 ± 24.57	0.006
Blood urea nitrogen (mmol/L), *M* (P_{25}, P_{75})	5.52 (4.52,7.10)	5.42 (4.31,6.59)	NS
Serum creatinine (umol/L), *M* (P_{25}, P_{75})	76 (62, 94)	72 (60, 88)	NS
Colonoscopy, n (%)	37 (31.6%)	191 (21.3%)	0.012

Notes: Continuous variables were presented by mean ± SD, or by median (interquartile range) in the case of a skewed distribution. Categorical variables were expressed as proportions. The group without the occurrence of hypoglycemia is termed as non-hypoglycemia group.

Abbreviations: NS, non-Significant; BMI, body mass index; DDP-4, dipeptidyl peptidase-4; SGLT2, Sodium-glucose cotransporter protein 2; HbA1c, Glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate.

Table 2 Analyzing the Association of Colonoscopy and Hypoglycemia Using Logistic Regression Analysis (n = 1016)

	With Colonoscopy	Without Colonoscopy	AOR (95% CI)		
			Model 1	Model 2	Model 3
Hypoglycemia No. (%)	37 (16.2%)	80 (10.1%)	1.75 (1.15–2.67)	1.81 (1.17–2.80)	1.99 (1.25–3.19)

Notes: Model 1 was adjusted for age and gender; Model 2 was adjusted for the length of hospital stay, disease duration, diabetic retinopathy, diabetic peripheral neuropathy, and diabetic nephropathy based on Model 1; Model 3 was adjusted for FBG, 2h PG, FCP, 2h CP, e-GFR, and insulin based on Model 2.
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

age of 57 (ranging from 18 to 91). Subjects with hypoglycemia had longer hospital stays and longer duration of diabetes. Insulin therapy is more common in those patients who have hypoglycemia than in those who do not. As for comorbidities, patients with hypoglycemia were more likely to have diabetic retinopathy, diabetic peripheral neuropathy, and diabetic nephropathy. Regarding biochemical parameters, the levels of FPG, 2h PG, FCP, 2h CP, and eGFR were lower in subjects with hypoglycemia than in those without hypoglycemia. As for colonoscopy, there was a significant difference in colonoscopy exposure between the two groups. The colonoscopy exposure rate in patients with hypoglycemia was significantly higher than that in patients without hypoglycemia (31.6% vs 21.3%, p = 0.012). Other covariates did not have differences between the two groups.

Hypoglycemia (BG < 3.9 mmol/L [70 mg/dL]) occurred in 80 of 788 (10.1%) patients without colonoscopy exposure and 37 of 228 (16.2%) patients with colonoscopy exposure. In 12 of the 37 patients (32.4%), hypoglycemia occurred between the beginning of bowel preparation and before colonoscopy, and in the remaining 25 patients (67.6%), hypoglycemia occurred from 3 hours to 68 hours after the end of colonoscopy. Patients fasted for 10–18 hours before colonoscopy. Patients with partially resected intestinal polyps resumed normal diet after 2–7 days.

After adjusting for the duration of diabetes, the length of hospital stay, diabetic retinopathy, diabetic peripheral neuropathy, diabetic nephropathy, insulin therapy, FPG, 2h PG, FCP, 2h CP, e-GFR, age, and gender, patients exposed to colonoscopy had an increased risk of 99% of hypoglycemia compared to those not exposed to colonoscopy (OR 1.99, 95% CI 1.25–3.19) (Table 2).

No significant inconsistencies were found in a range of subgroups related to gender, age, disease duration, glycated hemoglobin, or BMI. After adjusting for the length of hospitalization, duration of disease, diabetic retinopathy, diabetic peripheral neuropathy, diabetic nephropathy, FPG, 2h PG, FCP, 2h CP, e-GFR, insulin therapy, age, and gender, and excluding stratification factors, the association between colonoscopy and hypoglycemia was significant in patients who were females, overweight, aged ≥ 65, with disease duration ≥ 10 years, and with glycated hemoglobin > 7.0% (Figure 2).

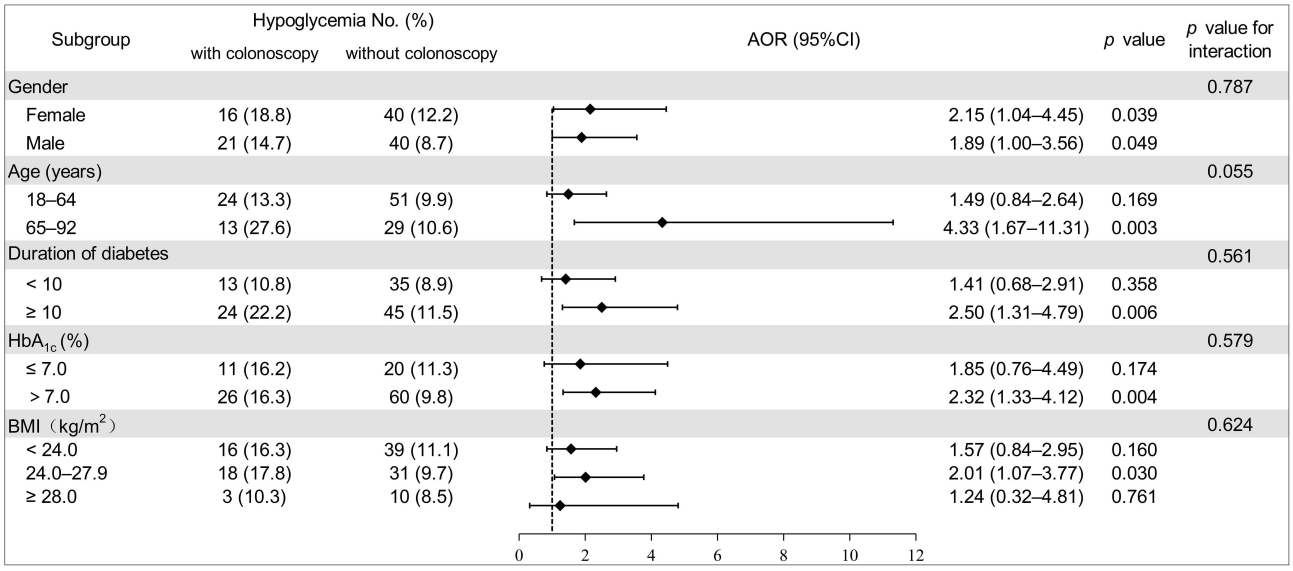

Figure 2 Subgroup analysis of the relationship between colonoscopy and hypoglycemia.
Abbreviations: HbA_{1c}, glycated hemoglobin; BMI, body mass index; AOR, adjusted odds ratio; CI, confidence interval.

Discussion

In this retrospective real-world study, colonoscopy was associated with a significantly increased risk of hypoglycemia during hospitalization in patients with T2DM. Adjusting for demographic and clinical risk factors, the risk of hypoglycemia in patients undergoing colonoscopy was 1.99 times higher than that in patients who did not undergo colonoscopy. The association was consistent in subgroups of females, the elderly, the overweight patients, patients with long duration of disease or patients with suboptimal glycemic control.

Our findings extended the epidemiology of the relationship between hypoglycemia and colonoscopy. The prevalence of hypoglycemia in T2DM patients undergoing colonoscopy was 16.2%, much higher than that of the previous studies (Hypoglycemic events were just recorded in 4 of 150 patients [2.7%]).[9] Two factors may account for this discrepancy. First, the hypoglycemia criteria were self-reported in previous studies, whereas our study data came from a more objective method using a point-of-care blood testing in capillary blood and recorded by the hospital's blood sugar management system; second, the study population of the previous study was limited, but our study included a larger number of inpatients and could more accurately examine the relationship between hypoglycemia and colonoscopy.

Our study also found that 67.6% of hypoglycemic events occurred after colonoscopy. This could be attributed to the fact that some participants are required to continue fasting or are unable to resume a regular diet after colonoscopy because of the removal of polyps. It has also been clinically observed that patients continue to have gastrointestinal problems such as diarrhea and abdominal pain after the end of colonoscopy, which may also contribute to the occurrence of hypoglycemia after the examination. Limited studies focus on patients' glycemic status after colonoscopy, but our study adds to the existing literature by demonstrating that diabetic patients are still at risk of hypoglycemia after colonoscopy, even within 68 hours after the end of the examination. Future research should focus on the fluctuation of glycemic status in patients with T2DM after colonoscopy.

The underlying mechanism for hypoglycemia in diabetic patients remains multifactorial and uncertain. The literature reports that hypoglycemia is mostly triggered by dietary modifications, including delayed or missed meals,[17] low carbohydrate intake, or fasting.[18] The day before the examination, patients are required to have a low-fiber diet, a high-carbohydrate dietary pattern contrary to the dieting habits of diabetic patients, which may affect their blood glucose status.[6] Patients undergoing colonoscopy must fast from 10 hours to 18 hours before the examination, and those who have had their polyps removed during the examination may take another 2 days to 7 days to resume a normal diet. Dietary modifications are likely to be a trigger for hypoglycemia in patients undergoing colonoscopy. It has been well documented that diabetes was related to adenomatous polyps.[19] On the other hand, as oral laxative is required before the examination, patients often suffer from diarrhea, abdominal pain, bloating, and other discomforts. All these digestive reactions can affect the patient's blood glucose and may be the cause of hypoglycemia.[20]

To further identify the association between colonoscopy and hypoglycemia, efforts have been made to adequately collect and adjust for several confounding factors associated with the increased risk of hypoglycemia when designing this retrospective analysis. However, this study, like any observational study, has certain limitations due to the complicated hypoglycemia risk factors. First, the baseline survey did not obtain all the exposure data, and several unmeasured variables (including prior hypoglycemia, cognitive impairment, and depression) were not included in the model adjustment, potentially leading to residual confusion; second, the research data were just obtained from a single center study in a Chinese population; third, hypoglycemia in this study was determined by point-of-care blood testing in capillary blood, and patients were monitored four times a day, therefore the incidence of hypoglycemia may be underestimated compared with more advanced methods such as continuous glucose monitoring. These shortcomings provide direction for subsequent studies on the relationship between hypoglycemia and colonoscopy.

Conclusion

Colonoscopy is associated with an increased risk of hypoglycemia in patients with T2DM. Given the increasing need for colonoscopy in patients with diabetes, and to avoid the impact of cardiovascular events on quality of life due to hypoglycemia, the patient's glycemic status should be closely monitored during the peri-colonoscopy cycle, even within

68 hours after the end of the colonoscopy. Future studies should examine the potential causal relationship between these observations.

Acknowledgments

We would like to express our sincere gratitude to our colleagues in the Endocrinology Department of Shenzhen Hospital of Traditional Chinese Medicine.

Funding

This work was funded by the Scientific Research Project of Traditional Chinese Medicine Bureau of Guangdong Province (No. 20211324).

Disclosure

The authors report no conflicts of interest in this work.

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