

Adjustment of Anti-Hyperglycaemic Agents During Bowel Preparation for Colonoscopy in Patients with Diabetes

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ABSTRACT

Objective Due to the growing diabetes pandemic, the number of colonoscopies performed in patients with diabetes is steadily rising. However, recommendations on adjustments of anti-hyperglycaemic agents (AHG) during bowel preparation for colonoscopy are limited.

Methods A total of nine articles were revealed on a PubMed search using the search terms “diabetes” and “colonoscopy”, “sigmoidoscopy”, “endoscopy”, “endoscopic intervention”, “endoscopic invasive diagnostics”, “endoscopic surgery”, or “diabetes care in the hospital” and manual screening of the references of the articles reporting on AHG adjustment during bowel preparation.

Results Regular glucose measurements and the opportunity to contact the diabetes team were commonly advised. Recommendations also agreed that all oral AHG and short-acting insulin should be omitted when patients are on clear fluids. Recent studies suggest discontinuation of sodium-glucose cotransporter-2 (SGLT2) inhibitors even three days before the colonoscopy. In contrast, recommendations differed regarding adjustment of basal insulin depending on diabetes type and time point in relation to the intervention.

Conclusions While discontinuation of oral AHG and short-acting insulin during bowel preparation for colonoscopy is generally accepted, recommendations on the adaptation of basal insulin follow different approaches.

Introduction

Colorectal cancer (CRC) is the third most common cancer in men, the second most common cancer in women and the third leading cause of cancer-related death worldwide, accounting for about 1.9 million new cases and 0.9 million deaths in 2018 [1]. Global mortality rates due to CRC increased by 57% from 1990 to 2013 [2]. Meanwhile, the

incidence of diabetes increased by more than 100%, from 11.3 million in 1990 to 22.9 million in 2017, resulting in a global diabetes prevalence of 476.0 million in 2017 [3]. Patients with type-2-diabetes (T2D) are at moderately increased risk of CRC, particularly in the presence of longer disease duration and comorbid obesity [4]. CRC and

T2D share common risk factors, such as obesity, sedentary lifestyle, high caloric diet, high red meat and low fibre intake [5, 6].

CRC is one of the few cancers for which several screening tools are available, including faecal occult blood tests, faecal immunochemical tests, flexible sigmoidoscopy and colonoscopy. Detection and removal of adenomatous polyps and identification of early disease stages bear the potential to significantly reduce CRC incidence and mortality [7, 8]. Therefore, structured opportunistic and population-based organised screening programs were implemented in European countries and the US [9]. Approximately 15 million colonoscopies are performed annually in the US and 0.9 million in the UK [10, 11].

Diabetes is an independent risk factor for inadequate bowel preparation [12], with slow intestinal transit and delayed gastric emptying as potential underlying mechanisms [13]. Poor bowel preparation for colonoscopy has deleterious effects, such as reduced identification of neoplastic or preneoplastic lesions, increased procedural time, higher risk of procedure-related adverse events and increased health care costs [14]. Furthermore, diabetes patients are at increased risk for metabolic derangements, such as hypoglycaemia, diabetic ketoacidosis and lactic acidosis, fluid and electrolyte imbalances, as well as an acute renal failure during bowel preparation [15]. However, recommendations for adjustments of anti-hyperglycaemic agents (AHG) during colonoscopy preparation are limited. This is of particular concern, as diabetes management in the peri-colonoscopy period may significantly differ between gastroenterology providers and expert endocrinologists [16].

The present review article aims at providing an overview of the existing literature on AHG adjustments during bowel preparation for colonoscopy in patients with diabetes.

Methods

Search strategy in PubMed and selection criteria for analysis

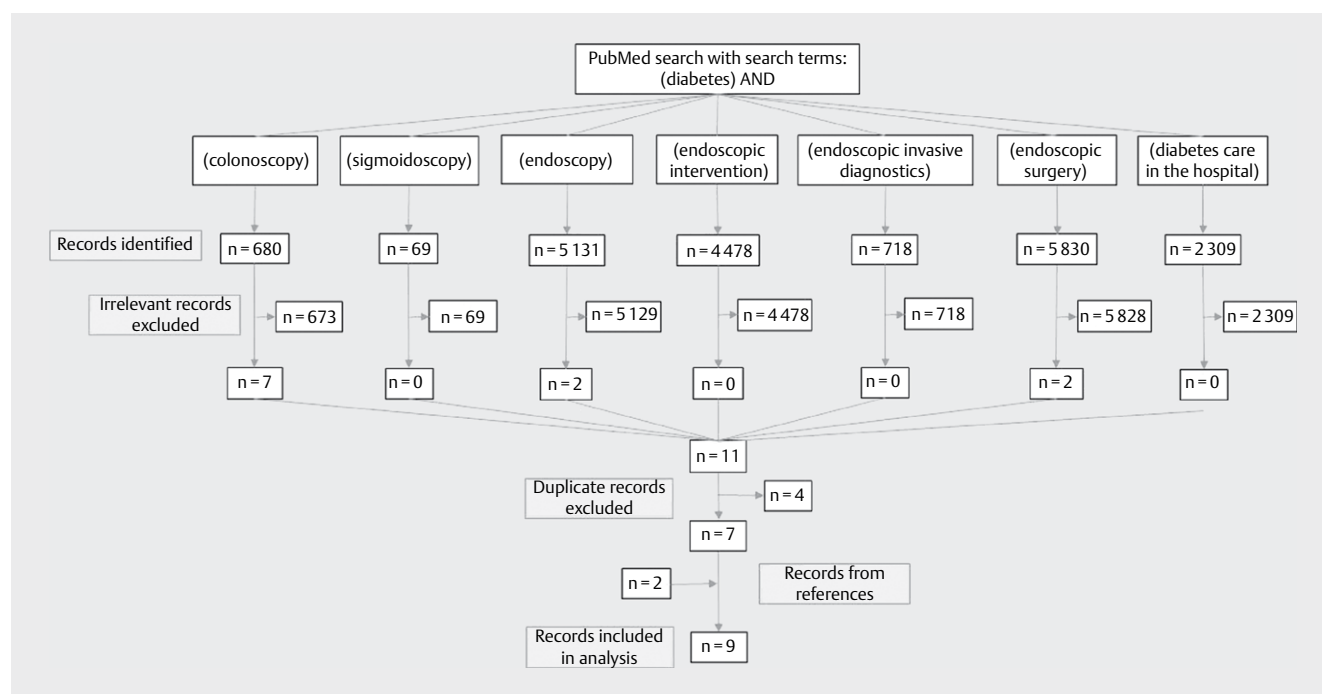
PubMed database was searched until 28th January 2022. The search terms “(diabetes) AND (colonoscopy)”, “(diabetes) AND (sigmoidoscopy)”, “(diabetes) AND (endoscopy)”, “(diabetes) AND (endoscopic intervention)”, “(diabetes) AND (endoscopic invasive diagnostics)”, “(diabetes) AND (endoscopic surgery)”, and “(diabetes) AND (diabetes care in the hospital)” were used. Only articles in English reporting on dose adjustments of AHG during bowel preparation for colonoscopy were considered. Subsequently, references of included articles were manually screened for relevant articles.

Results

As shown in ► **Fig. 1**, 19,215 articles were retrieved, of which seven reported on dose adjustments of AHG during bowel preparation for colonoscopy. The electronic search was supplemented by a manual screening of the references of included articles. Out of 91 citations, we included the peri-operative diabetes management guidelines of the Australian Diabetes Society [17] and an alert update on periprocedural diabetic ketoacidosis (DKA) with sodium-glucose cotransporter-2 (SGLT2) inhibitor use by the Australian Diabetes Society [18].

AHG adjustments during colonoscopy preparation

The Israeli position statement [19] and the peri-operative diabetes management guidelines of the Australian Diabetes Society agree that all oral AHG should be omitted while patients are on clear fluids (► **Table 1**). Furthermore, the Israeli position statement suggests discontinuation of sulfonylureas and SGLT2 inhibitors on the day before



► **Fig. 1** The search strategy used in this study.

► **Table 1** Suggested instructions for adjustments of glucose-lowering medications during preparation for colonoscopy.

Treatment type	Israeli position statement [19]		Australian Diabetes Society [17]
	Day before colonoscopy	Day of colonoscopy	While patients are on clear fluids
Sulfonylureas SGLT2 inhibitors	Do not take.	Do not take until resuming regular meals.	Omit all AHG.
Metformin Meglitinides Acarbose Thiazolidiones DPP-4 inhibitors GLP-1R agonists	Take as long as eating solid food.	Do not take until resuming regular meals.	
Basal insulin Premixed rapid/short and medium insulin Combined basal insulin + GLP-1R agonists	Take the usual dose until 24 hours before the colonoscopy. In the 24 hours before colonoscopy: Type 1 diabetes patients: Inject 50 to 80 % of usual dose; consult diabetes clinic. Type 2 diabetes patients: Inject 50 % of usual dose.	Type 1 diabetes patients who inject in the morning: Inject 50 to 80 % of usual dose; consult diabetes clinic. Type 2 diabetes patients: Do not inject until resuming regular meals.	
Rapid insulin in pens or insulin pump	Continue usual dose as long as eating solid food. Thereafter, if glucose is more than 200 mg/dl (11 mmol/L), give only corrections as the patient does in other fasting situations.	Do not take until resuming regular meals.	Omit short-acting insulin when given in combination with glargine or detemir/isophane twice daily. ½ sum of all mealtime short-acting insulin and administer as detemir/isophane in the morning when given in combination with detemir/isophane at night only.
Insulin pump	When discontinuing solid food, reduce basal insulin. Type 1 diabetes patients: Reduce to 50 to 80 % of usual dose; consult diabetes clinic. Type 2 diabetes patients: Reduce to 50 % of usual dose.	Continue reduced dose until resuming regular meals. Leave insulin pump on during colonoscopy. Intravenous glucose should be given if needed. Resume the usual dose when resuming regular meals.	Continue at the basal infusion rate.

AHG, antihyperglycemic; DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; SGLT2, sodium-glucose cotransporter-2

the colonoscopy, independent of food intake. A recent case series reported eight patients with T2D treated with SGLT2 inhibitors who developed mild to severe ketoacidosis during bowel preparation for colonoscopy [20]. All but one patient took their SGLT2 inhibitor on the morning of the procedure. The authors suggested that SGLT2 inhibitors should be stopped at least two days prior to colonoscopy. In accordance with the Israeli position statement and the guidelines of the Australian Diabetes Society, adequate hydration and calorie intake during bowel preparation were encouraged to avoid fluid or electrolyte shifts (► **Table 2**). The Australian Diabetes Society guidelines suggest the addition of extra glucose in fluid if blood glucose levels fall below 90 mg/dL (5 mmol/L) and to avoid diet drinks or diet jelly unless blood glucose levels exceed 180 mg/dL (10 mmol/L). Meyer et al. recommended testing for metabolic acidosis by blood gas analysis in case of a finger-prick ketone of more than 1.0 mmol/L. In patients with confirmed acidosis, i. e., a base excess of less than -5, treatment with intravenous insulin and glucose infusion was suggested. This case series prompted the Australian Diabetes Society to publish a clinical alert update on periprocedural DKA with SGLT2 inhibitor use [18]. For colonoscopy requiring bowel preparation, ceasing of SGLT2 inhibitor intake at least three days pre-procedure and the day of the procedure was recommended. This is in line with the current clinical practice recommendation of the American Diabetes

Association (ADA) that recommends discontinuation of SGLT2 inhibitors three days before surgery [21]. According to the Australian Diabetes Society, SGLT2 inhibitor intake should only be recommended in patients on full oral intake. Blood ketone levels should be measured on admission. A colonoscopy can be performed if ketone levels are below 1.0 mmol/L and the patient is clinically well. The suggested management in clinically well patients who have not stopped SGLT2 inhibitors is mentioned in ► **Table 3**. A very recent cross-sectional study on the capillary ketone concentrations at the time of colonoscopy suggested 1.7 mmol/L as the cut-off point, in light of a reference range for capillary ketone concentrations in normoglycaemic people undergoing colonoscopy of 0.0–1.7 mmol/L [22]. However, according to Thiruvengatarajan et al., the proposed change of the cut-off appears to be premature, given that the analysis was based on a non-normally distributed data set, bearing the risk of high variability and reduced reliability [23]. Furthermore, the analysis comprised only metabolically healthy people, not allowing conclusions for diabetes patients, as the risk for developing ketoacidosis might be different in metabolically healthy people and patients with diabetes. In addition, a higher threshold may decrease the detection rate of early ketoacidosis, making it difficult to prevent severe ketoacidosis. In their response, Hamblin et al. argued that the cut-off of a β -hydroxybutyrate concentration of > 1.0 mmol/L is, in contrast

► **Table 2** Suggested glucose monitoring, diet, and further recommendations while patients are on clear fluids.

	Israeli position statement [19]	Australian Diabetes Society [17]
Blood glucose monitoring	Patients should frequently monitor their glucose levels, insulin-treated patients at least every four hours after the last solid meal until resuming eating.	More frequent BGL monitoring (every 2 hours).
Diet	The clear-liquid phase should include not only water but also liquids containing electrolytes such as broth and clear juice.	May consume glucose-containing fluid or jelly. Add extra glucose in fluid if BGL < 90 mg/dL (5.0 mmol/L). Avoid diet drinks or diet jelly unless BGL > 180 mg/dl (10 mmol/L).
Timing of procedure	Mid-morning scheduling (after 9:30 a.m.) improves bowel preparation in patients with diabetes.	
Hospital admission		Consider admitting patients with unstable glycaemic control to the hospital during the period of clear fluid.
Diabetes team	Type 1 diabetes patients should consult a diabetes clinic for dose adjustments of basal insulin.	Patients must have access to their diabetes physician or diabetes centre for advice.
BGL, blood glucose		

► **Table 3** Suggested management of clinically well patients who have not ceased sodium-glucose cotransporter-2 (SGLT2) inhibitors (modified after [18]).

Ketones (mmol/l)	Base Excess	Comments
< 1	> -5	No ketosis and no metabolic acidosis.
		Consider proceeding with the procedure: hourly monitoring of blood ketones during the procedure, and 2 nd hourly following the procedure until eating and drinking normally or discharged. Provide the patient with written post-discharge advice. Where blood gas analysis is not available, proceed only if the added risk is consistent with goals of care.
> 1	> -5	Ketosis without metabolic acidosis.
		Seek endocrinology advice. Ketosis without acidosis may reflect starvation, particularly in patients with HbA1c < 9% (< 75 mmol/mol). Consider proceeding, but with periprocedural insulin and dextrose infusions to reduce the risk of ketosis and acidosis (DKA).
> 1	< -5	Ketosis with metabolic acidosis.
		Strongly consider postponing procedure. Escalate care with endocrinology and critical care.
Blood gas analysis is recommended to assess for the presence of metabolic acidosis. Where blood gas analysis is not readily available and the ketones are > 1.0 mmol/l, the procedure should not be performed.		

to the proposed cut-off of > 1.7 mmol/L, not evidence-based. Besides, a lower threshold may increase the number of cancelled colonoscopies [24]. This would be of particular concern, as patients with diabetes are at increased risk of colorectal adenomas [25] and screening colonoscopies were reported to be associated with a 17% lower mortality risk from colorectal cancer [26].

Cardiologists are increasingly prescribing SGLT2 inhibitors for treating heart failure, in accordance with the recently published 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure [27], and by nephrologists for treating chronic kidney disease, in line with the UK Kidney Association clinical practice guideline on SGLT2 inhibition in adults with kidney disease [28]. Therefore, the recommendations regarding cessation of SGLT2 inhibitors before colonoscopy apply not only for patients with diabetes but also for other patient groups taking SGLT2 inhibitors.

The Israeli position statement, as well as the Australian Diabetes Society guidelines, suggest discontinuation of short-acting insulin when solid foods are not taken. Only if blood glucose levels are increased to more than 200 mg/dL (11 mmol/L) corrections should be performed as in other fasting situations. Alternatively, according to the Australian Diabetes Society guidelines, half of the

sum of meal-time insulin can be given as detemir/isophane in the morning if meal-time insulin is given regularly in combination with detemir/isophane at night only.

In contrast, the recommendations regarding basal insulin differ between the Israeli position statement and the Australian Diabetes Society guidelines. The latter suggests continuing glargine, detemir/isophane twice daily or in the evening/night, as well as basal infusion rate in insulin pump users. Whereas, the Israeli position statement recommends dose reductions of basal insulin depending on the diabetes type. Patients with type 1 diabetes (T1D) should inject 50 to 80% of the usual dose on the day before the colonoscopy as well as on the day of the colonoscopy. By contrast, patients with T2D should inject 50% of the usual dose on the day before colonoscopy and should not inject basal insulin on the day of colonoscopy until resuming regular meals. This is in line with a previous study on patients with T2D treated with the ultra-long acting insulin analogue degludec. Patients underwent colonoscopy safely when degludec was discontinued only once on the day of the procedure. None of the patients suffered from hypoglycaemia during the fasting period on the day of colonoscopy [29].

Regular blood glucose monitoring during bowel preparation is recommended by the Israeli position statement (at least every four

hours) as well as by the Australian Diabetes Society guidelines (every two hours) (► **Table 3**). To improve bowel preparation in patients with diabetes, the Israeli position statement recommends that colonoscopy should be scheduled after 9:30 a.m., whereas the Australian Diabetes Society guidelines do not contain recommendations regarding the scheduling of the procedure. However, the Australian Diabetes Society guidelines suggest hospital admission of patients with unstable diabetes during the period of bowel preparation. The Australian Diabetes Society guidelines and the Israeli position statement agree that, in particular, patients with T1D must have the opportunity to consult their diabetes team.

Conclusions

A thorough peri-interventional diabetes management allows preparation for colonoscopy in patients with diabetes having no clinically relevant adverse events [30]. However, only a very limited number of recommendations on adjustment of glucose-lowering medication during bowel preparation for colonoscopy is found in the literature. These recommendations agree on the necessity of regular glucose measurements, dose adaptation or discontinuation of oral AHG or short-acting insulin and the opportunity to contact the diabetes team, but differ regarding the adaptation of basal insulin depending on diabetes type and time point in relation to the intervention.

In general, only a few recommendations for altering diabetes medication in special situations have been reported, whereas, for some medications, there are abundant recommendations how to adjust their dosages in certain situations, such as adjustments of antithrombotic/anticoagulation medication prior to surgery [31]. Leading medical societies for diabetes as well as for gastroenterology have published recommendations or guidelines for adjusting diabetes medication during acute illness, in an inpatient hospital situation, or during fasting and surgical procedures [21], but, except for the guidelines of the Australian Diabetes Society [17], explicit recommendations of medical societies or associations for the handling of diabetes medication in preparation for colonoscopy are still lacking. This gap needs to be filled by developing such recommendations in an interdisciplinary approach between gastroenterologists/endoscopists and diabetologists/endocrinologists. This would significantly contribute to improving safety aspects of routine procedures and diagnostics as well as treatment outcomes for a considerable cohort of patients.

Author contribution statement

K.M. wrote the manuscript and researched the data. H.E.A. researched the data, contributed to the discussion, and reviewed/edited the manuscript. All authors critically reviewed the manuscript. K.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Conflict of Interest

The authors have no conflict of interest to declare.

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