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Body Mass Index is inversely associated with capillary ketones at the time of colonoscopy: Implications for SGLT2i use

Running title: Ketones and colonoscopy

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Summary

Objective

SGLT2 inhibitors (SGLT2i) have been associated with diabetic ketoacidosis at the time of colonoscopy. This study aimed to identify factors associated with ketone concentrations in SGLT2i-treated type 2 diabetes compared with non-SGLT2i-treated diabetes, and those with impaired fasting glycaemia (IFG) and normoglycaemia.

Design

Cross-sectional, multi-centre, observational study June-December 2020 in four Australian tertiary hospitals.

Participants

Capillary glucose and ketones were measured in people undergoing colonoscopy: 37 SGLT2i-treated and 105 non-SGLT2i-treated type 2 diabetes, 65 IFG and 151 normoglycaemia.

Measurements

BMI, age, glucose, fasting duration and where relevant, HbA1c and time since last SGLT2i dose.

Results

In SGLT2i-treated diabetes, BMI (ρ= -0.43 (95% CI -0.67, -0.11)) and duration since last SGLT2i dose (ρ= -0.33 (-0.60, 0.00)) correlated negatively with increasing ketones, but there was no correlation with fasting duration. In non-SGLT2i-treated diabetes, BMI correlated negatively (ρ= -0.24 (-0.42, -0.05)) and fasting duration positively (ρ=0.26 (0.07, 0.43)) with ketones. In IFG participants, only fasting duration correlated with ketones (ρ=0.28 (0.03, 0.49)). In normoglycaemic participants, there were negative correlations with BMI (ρ= -0.20 (-0.35, -0.04)) and fasting glucose (ρ= -0.31 (-0.45, -0.15)) and positive correlations with fasting duration (ρ=0.20 (0.04, 0.35)) and age (ρ=0.19 (0.03, 0.34)). Multiple regression analysis of the entire cohort showed BMI, age and fasting glucose remained independently associated with ketones, but in SGLT2i-treated participants only BMI remained independently associated.

Conclusions

In SGLT2i-treated diabetes, lower BMI was a novel risk factor for higher ketones pre-colonoscopy. Pending larger confirmatory studies, extra vigilance for ketoacidosis is warranted in these people.

Key words

Sodium-Glucose Transporter 2 Inhibitors; Diabetic Ketoacidosis; Diabetes Mellitus, Type 2; Ketones; Ketosis; Colonoscopy; Impaired fasting glycaemia

Introduction

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are increasingly being used for people with type 2 diabetes, given their cardio-renal benefits (1-5). Colonoscopies are common, with one in 32 Australians and 19 million Americans having this procedure in 2017 (6, 7). Type 2 diabetes is a risk factor for colorectal cancer (8, 9). It is therefore not surprising that increasing numbers of people undergoing a colonoscopy are taking SGLT2i, and this will likely increase, given their benefits in cardiac failure and renal disease irrespective of diabetes (10-13). People with diabetes are at increased risk of SGLT2i-associated diabetic ketoacidosis (DKA) (14-16) and there have been case reports of DKA associated with colonoscopy and SGLT2i-treated diabetes (17). It is not currently known if people treated with SGLT2i who do not have diabetes are also at risk.

Fasting and dehydration are prominent risk factors for SGLT2i-associated DKA (16). However, as case series describe emergency presentations, the duration of fasting and timing of the last dose of SGLT2i are often poorly documented. In contrast, fasting duration and timing of the last SGLT2i dose are known in patients undergoing

colonoscopy. Colonoscopy preparation therefore provides an excellent opportunity to assess the factors that are associated with capillary ketone concentrations in a controlled manner. Further, it is clinically important to identify people at increased risk of developing elevated capillary ketone concentrations at the time of colonoscopy while being treated with SGLT2i as they are more likely to be at risk of developing DKA.

We recently determined the capillary ketone concentration reference interval for normoglycaemic individuals undergoing colonoscopy as 0-1.7 mmol/L with 9% having levels > 1.0 mmol/L (18). The aim of the current study was to extend this work by examining potential factors associated with elevated capillary ketone concentrations in people with SGLT2i-treated type 2 diabetes and compare them with people who had non-SGLT2i-treated type 2 diabetes, impaired fasting glycaemia (IFG) and normoglycaemia.

Materials and Methods

This cross-sectional multi-centre observational study of community dwelling adults admitted as day patients for colonoscopy was conducted between June and December 2020 at four tertiary health services (Alfred, Austin, Eastern and Western Health) in Melbourne, Australia, a multicultural city of 5 million people (18).

There were four pre-specified groups: participants with SGLT2i-treated type 2 diabetes, non-SGLT2i-treated diabetes, IFG and normoglycaemia. Three groups were included in our previous work (18) and the IFG group was added for analysis in this study. Based on fasting capillary blood glucose obtained at the time of colonoscopy, in participants with no history of diabetes, normoglycaemia was defined as < 5.5 mmol/L and IFG as 5.6 - 6.9 mmol/L inclusive. Given the current advice to withhold

SGLT2i for three days before a colonoscopy (19), participants were assigned to the SGLT2i-treated diabetes group if any dose had been taken within 80 hours of the colonoscopy. This allowed for inclusion of participants whose colonoscopy was scheduled for an afternoon list who may have taken their last dose in the morning three days before the procedure. Participants with non-SGLT2i-treated diabetes were treated by diet alone or any oral or injectable hypoglycaemic agent except SGLT2i. In addition, three participants who were usually treated with SGLT2i but had taken their last dose more than 80 hours before the colonoscopy were assigned to the non-SGLT2i-treated group. No participant received oral or intravenous carbohydrate while waiting for their colonoscopy.

Exclusion criteria in all groups were a history of type 1 diabetes, pancreatitis, pancreatic cancer, pancreatic surgery, hemochromatosis, cystic fibrosis, starvation ketosis (defined as anyone fasting for longer than 72 hours) and pregnancy.

Demographic, clinical and biochemical data

Standard demographic data, indications for colonoscopy, and the number of hours since the last consumption of any food and/or carbohydrate-containing fluids were recorded. Participants' self-reported weights and heights were documented by study researchers. BMI was then calculated. To assess whether volume depletion was a factor in the potential development of ketosis, the type of bowel preparation was ascertained. Standard bowel preparation consisted of either oral Moviprep (Macrogol 3350, potassium chloride, sodium chloride, sodium sulphate, ascorbic acid; sodium ascorbate) or oral Picoprep (sodium picosulfate, magnesium oxide, citric acid) + Glycoprep (sodium chloride, potassium chloride, ascorbic acid, sodium sulphate, Macrogol 3350). Extended bowel preparation consisted of the standard bowel

preparation but double the usual volume of Glycoprep and/or an extra five days of oral Movicol (Macrogol 3350 with electrolytes) and/or a rectal Fleet enema (sodium biphosphate and sodium phosphate) in the hour before the colonoscopy.

For participants with type 2 diabetes, duration of diabetes, diabetes medications and HbA1c within the preceding 12 months were recorded. Where relevant, timing of the last SGLT2i dose was obtained. For insulin users, the type of insulin and time of the last dose of insulin was also obtained.

Measurement of capillary glucose and ketone concentrations

Point-of-care capillary glucose and ketone concentrations were measured in all participants less than 90 minutes prior to colonoscopy, using either Nova Biomedical meters (two study sites) or Abbott Freestyle Optium Neo meters (two study sites). These are the standard meters regularly used at the study hospitals. Finger-prick capillary testing, procedures for storage, handling of test strips and regular meter quality assurance were performed in accordance with the manufacturers' recommendations.

Nova Biomedical StatStrip glucose test strips have a blood glucose measurement range of 0.6 - 33.3 mmol/L, with a coefficient of variation (CV) < 5%. Abbott Freestyle Optium Neo blood glucose test strips have a blood glucose range of 1.1 - 27.8 mmol/L, CV < 6%. Nova StatStrip ketone test strips and Abbott ketone test strips both measure beta-hydroxybutyrate, and both have a measurement range of 0 - 8.0 mmol/L with a CV < 5.5% (20).

Statistics

Data were analysed using IBM SPSS Statistics version 27. Normally distributed data are reported as mean ± SD, whereas non-normally distributed continuous data are reported as median (interquartile range, IQR). Normally distributed characteristics of participants in the four groups were compared by one-way ANOVA followed by Bonferroni correction for post-hoc multiple comparisons. Chi-square test was used for categorical variables with Bonferroni correction for post-hoc multiple comparisons. Differences between non-SGLT2i-treated and SGLT2i-treated participants were analysed by unpaired t-test.

Since ketone concentrations were not normally distributed, non-parametric methods were used. To assess possible bias due to population and/or analytical differences, the Kruskal-Wallis test was used to compare capillary ketone concentration distributions across the four centres and the Mann-Whitney U test was used to compare distributions using the two analytical methods. Spearman correlation analysis was used to determine associations with capillary ketone concentrations.

Multiple regression analysis was used to determine independent associations of participant group, BMI, age, glucose and duration of fasting with ketone concentrations in the entire cohort and HbA1c in the diabetes groups. A separate analysis of SGLT2i-treated participants included time since last SGLT2i dose as a variable.

Ethics

Multi-site ethics approval was granted by the Alfred Human Research Ethics Committee (HREC/61222/Alfred-2020) and local research governance approval was obtained at each site before study commencement.

Results

The recruitment flowchart is shown in Figure 1. Three hundred and seventy two people were invited to participate, with the aim of recruiting a minimum of 120 normoglycaemic participants to ascertain a normal reference range (21). Fourteen were excluded for the reasons outlined (Fig. 1). As previously reported (18), 37 had SGLT2i-treated type 2 diabetes, 105 had non-SGLT2i-treated type 2 diabetes, (102 not usually treated with SGLT2i and three who had taken their last SGLT2i doses 99, 102 and 168 hours before colonoscopy) and 151 had normoglycaemia. SGLT2i-treated participants had taken their last SGLT2i dose 59 + 17 hours (mean + SD) before the colonoscopy, with a range of 14-77 hours (18). Additionally, 65 participants with IFG were recruited contemporaneously.

The major indications for colonoscopy were similar between the four groups: rectal bleeding, positive faecal occult blood testing, surveillance and/or removal of colonic polyps and surveillance of previous colonic carcinoma.

Table 1 shows the characteristics of the participants. Those with diabetes and IFG were older ($p<0.001$) and had higher BMI ($p<0.001$) than those with normoglycaemia. There was a lower proportion of males in the IFG group compared to the SGLT2i-treated group. Participants were predominantly Caucasian with ethnicity being similar across the groups. Use of standard versus extended bowel preparations was similar between groups. Diabetes duration and HbA1c were similar in the diabetes groups.

There were no differences in distribution of capillary ketone concentrations among the four centres ($p=0.43$), and no differences between Abbott and Nova meters

(p=0.23). These findings suggest that there were no substantial population or analytical differences between centres.

Ketone concentrations differed significantly between groups (p=0.001), with lower levels in participants with IFG than in normoglycaemic participants and those taking SGLT2i (Table 1). Sex and type of bowel preparation were not associated with ketone levels in any individual group or in the combined cohort. As previously reported, one participant in the normoglycaemic group had a venous pH of 7.27 (ketones 1.6 mmol/L, blood glucose 3.5 mmol/L). Her colonoscopy and recovery period were uneventful. No other participant had venous pH < 7.30 (18).

In SGLT2i-treated participants, BMI (ρ= -0.43 (95% CI -0.67, -0.11)) and duration since last SGLT2i dose (ρ = -0.33 (-0.60, 0.00)) negatively correlated with ketone concentrations, whereby lower BMI values were associated with higher ketone levels (Figures 2, 3, Table 2). All three SGLT2i-treated participants with ketone concentrations above the upper limit of the normoglycaemic reference range of 1.7 mmol/L had BMI < 25 kg/m^2. In a multiple regression analysis of SGLT2i-treated participants, lower BMI was the only variable independently associated with ketone concentrations (Table 3).

In the normoglycaemic group, ketone concentrations negatively correlated with fasting glucose concentration (ρ = -0.31 (-0.45, -0.15)) and BMI (ρ = -0.20 (-0.35, -0.04)) and positively with fasting duration (ρ = 0.20 (0.04, 0.35)) and age (ρ = 0.19 (0.03, 0.34)). In the non-SGLT2i diabetes group, there was also a negative correlation with BMI (ρ = -0.24 (-0.42, -0.05)) and a positive correlation with fasting duration (ρ = 0.26 (0.07, 0.43)). In contrast, only fasting duration positively correlated with ketone concentrations in the IFG group (ρ = 0.28 (0.03, 0.49)).

In the entire cohort there was also a significant negative correlation between BMI and ketones (ρ = -0.22, $p<0.001$). In a multiple regression analysis, SGLT2i use and IFG were positively and negatively associated with ketone concentrations respectively (Table 4). After accounting for patient group, age retained an independent positive association, while fasting glucose and BMI retained independent negative associations with ketone concentrations.

Despite guidelines to withhold SGLT2i, 31 participants nevertheless took them 72 hours or less before the procedure, with marked variability in ketone concentrations (Fig. 3). Indeed, levels varied from 0.1 - 2.4 mmol/L at 72 hours, with six participants having ketone concentrations > 0.6 mmol/L and two with concentrations > 1.0 mmol/L. In contrast, two SGLT2i-treated participants had no detectable capillary ketones 40 and 54 hours since the last dose.

Of the 105 participants in the non-SGLT2i-treated group, 22 (21%) were also taking insulin, with the last insulin dose taken 18.8 ± 11.1 hours prior to colonoscopy (10 had a dose of pre-mixed insulin, 7 basal insulin, 4 both basal and fast acting insulin, and 1 fast acting insulin only). In the SGLT2i-treated group, six of the 37 (16%) were taking insulin, with the last dose (4 pre-mixed insulin and 2 basal insulin) 28.3 ± 19.5 hours prior to colonoscopy (p=0.30 vs non-SGLT2i). There was no correlation in either group between ketone concentrations and the time since the last insulin dose. In the non-SGLT2i group, there was no difference in ketone concentrations between insulin-treated and non-insulin treated participants (p=0.94) and no correlation between HbA1c levels and capillary ketone concentration. Numbers were too small to perform these analyses in the SGLT2i group. When both diabetes groups were combined, there

was also no correlation between HbA1c and ketone concentration (ρ = 0.082, p=0.34).

Discussion

The key finding of this study is that lower BMI was independently associated with higher ketone concentrations in the SGLT2i group and also the entire study cohort. This is a novel finding. Additionally, age and fasting glucose were also independently associated with ketone concentrations after accounting for patient group.

Univariate analysis showed that a number of factors correlated with ketone concentrations in individual groups. In SGLT2i-treated participants, BMI and duration since last SGLT2i dose were negatively correlated with ketone concentrations. In the non-SGLT2i diabetes group, BMI and fasting duration correlated negatively with ketone concentrations. Only fasting duration was correlated positively with ketone concentrations in the IFG group. In the normoglycaemic group, ketone concentrations correlated negatively with BMI and fasting glucose level and positively with age and fasting duration. Although each of the above individual correlations was weak to moderate, multiple regression analysis showed that they accounted for 16% and 38% of the variability in ketone levels in the entire cohort and SGLT2i group respectively.

The negative correlation observed between BMI and capillary ketone concentrations is an interesting finding. A small study comparing non-diabetic lean and age-matched obese women also described lower ketone concentrations in the obese group, postulated to be related to lower production of ketone bodies in obese compared to lean women (22). Another study investigating obesity-related non-alcoholic fatty liver

disease (NAFLD) found that ketone concentrations were lower in the obese group with NAFLD compared to a less obese group without NAFLD (23). Ketogenesis may be a proxy for hepatic fat oxidation and ketogenesis may be impaired as NAFLD progresses. Through incompletely understood mechanisms, hyperinsulinaemia suppresses ketogenesis in obese individuals and possibly contributes to lower ketones compared to lean controls (24). Similarly, in the diabetes groups, higher ketone concentrations may relate to lower C-peptide and insulin concentrations observed in people with type 2 diabetes who have lower BMI compared to those with higher BMI (25, 26).

While longer duration since the last SGLT2i dose correlated positively with lower capillary ketone concentrations, the association was weak and, because of marked inter-participant variability, not robust enough to be clinically reassuring. Whether the variability reflects individual differences in drug clearance and/or other mechanisms relating to ketone production remains to be determined (27-30).

Some guidelines state that SGLT2i-treated patients with HbA1c > 9% (75 mmol/mol) may have a greater risk of peri-procedural DKA (19). However, this suggestion does not appear to be evidence-based. In this study we did not observe a correlation between HbA1c and capillary ketone concentrations in SGLT2i-treated or non-SGLT2i treated participants, or for the combined diabetes groups. However, it should be noted that only 8% of the SGLT2i-treated participants and 12% of the non-SGLT2i-treated participants had HbA1c > 9% (75 mmol/mol).

Several confounding factors may account for the lack of associations with ketones in some groups. For example, the lack of association with fasting glucose in participants with diabetes may reflect the use of hypoglycaemic agents with variable efficacy in

modulating ketone production. In particular, the specific action of SGLT2i in promoting ketosis may have obscured relationships with other variables. Nevertheless, it is surprising that no relationship was observed with insulin treatment. As noted below, this may be due to the small sample size. Furthermore, the absence of associations in the IFG group may be due to the constrained glucose range by definition as well as lower ketone concentrations; the reasons for the latter require further study. Alternatively, statistical power to detect associations was limited by the smaller sample sizes of the IFG and SGLT2i groups.

Patients treated with SGLT2i may be at increased risk of ketosis and ketoacidosis when undergoing colonoscopy due to a period of fasting and the potential for dehydration due to the bowel preparation. It is unknown whether the negative association of BMI with ketone concentrations observed in the present study is specific for the colonoscopy situation or whether this is a more general association. Although the specific type of bowel preparation was not associated with ketone concentrations, the overall role of these preparations in promoting ketosis is not known, nor is the time-course of ketone production before and after the procedure.

Strengths and Limitations

The 358 participants were studied using a well-defined, predetermined protocol across four centres in geographically distinct parts of Melbourne with variable socio-economic characteristics. The use of two different brands of meter could be considered a strength, as it adds to the generalisability of the findings. The study participants were predominantly Caucasian. It is possible that there may be ethnic differences in ketogenesis (31), so our findings may not be applicable to other ethnic groups. It is also possible that some of the five SGLT2i-treated participants with BMI

< 25 kg/m^2 may have had undiagnosed latent auto-immune diabetes of adults, rather than type 2 diabetes. However, the age of this small subgroup (65 ± 8.4 years (mean ± SD)) and their long duration of diabetes (16.8 ± 8.4 years), with none requiring insulin treatment, make this unlikely. A study limitation is the use of self-reported heights and weights which may have underestimated BMI, especially for those with BMI > 28 kg/m^2 and overestimated those with BMI < 22 kg/m^2 (32). As mentioned above, the SGLT2i-treated diabetes and IFG groups were relatively small as was the insulin-treated cohort, so caution should be exercised when interpreting the results in those groups.

Conclusion

In multiple regression analysis of the entire cohort, after accounting for patient group, ketone concentrations were independently associated with BMI, age and fasting glucose. However in the SGLT2i group, only BMI remained independently associated with ketone concentrations. Pending larger, confirmatory studies, people undergoing colonoscopy with SGLT2i treated diabetes warrant clinical vigilance if they have a lower BMI, as they may be at increased risk for diabetic ketoacidosis.

Conflicts of Interest: SB, AF, PSH, RH, TPH, SNK, AM, MN, SR, and SSM report no conflicts. LAB was an investigator in DECLARE-TIMI 58. EIE's institution has received research funding from Novo Nordisk, Sanofi, Eli Lilly, Gilead and Bayer. EIE has served on the advisory boards of Sanofi, Eli Lilly and Pfizer, with the consultancy fees for these donated towards diabetes research at EIE's institution. EIE has received a travel grant from Boehringer to attend ADA virtual conference. RW has received speaker fees from Amgen.

Author contributions

PSH designed and co-ordinated the study, researched data and wrote the manuscript. RW contributed to study design, co-ordinated a site, researched data and wrote the manuscript. RH and SSM each co-ordinated a site, researched data and revised the manuscript. SB, AF, TPH, SNK, MN, SR researched data and revised the manuscript. AM and EIE contributed to study design and revised the manuscript. LAB contributed to study design, performed statistical analyses and revised the manuscript.

Peter Shane Hamblin takes responsibility for the contents of this article.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

Figure 1. **Recruitment Flowchart**

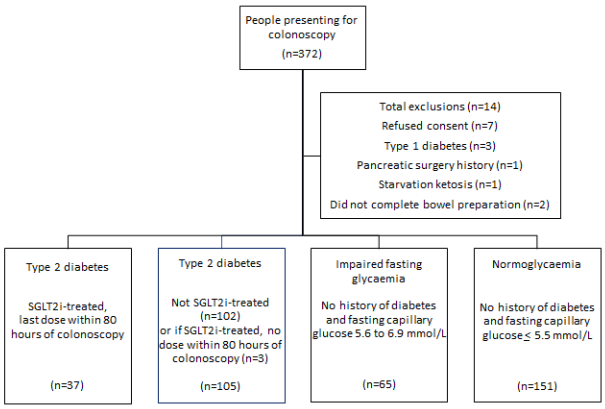

Figure 2. **Relationship between capillary ketone concentration and body mass index (BMI)**

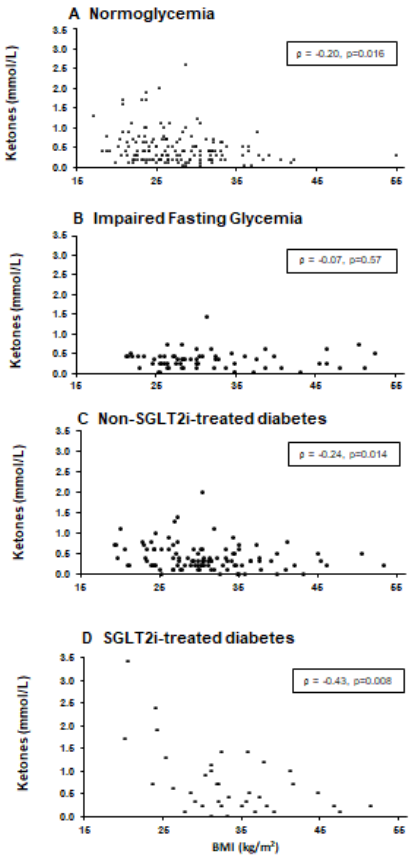

Figure 3. **Relationship between capillary ketone concentration and time of last SGLT2i dose**

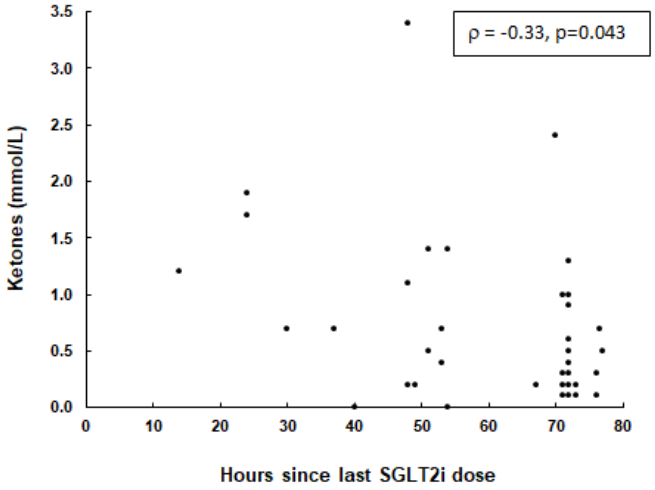

Table 1. **Characteristics of participants**

	Normoglycaemia (n = 151)	**Impaired Fasting Glucose (n=65)**	**Type 2 diabetes (non-SGLT2i) (n = 105)**	**Type 2 diabetes (with SGLT2i) (n = 37)**	**Overall p-value**
Age (y, mean ± SD)	53.8 ± 14.0	62.3 ± 10.8[a]	67.1 ± 11.0[a]	64.4 ± 10.6[a]	<0.001
Sex (% male)	60	43[b]	53	70	0.031
Ethnicity (%)					0.42
Caucasian	82	85	72	78	
Asian	15	11	18	14	
Middle Eastern	3	1	5	5	
African	1	3	1	5	
Pacific	0	0	4	0	

Islander/Maori					
BMI (kg/m^2, mean ± SD)	27.4 ± 5.7	31.6 ± 7.7 [a]	31.0 ± 6.6 [a]	33.4 ± 7.3 [a]	<0.001
*Fasting duration (h, mean ± SD)	18.6 ± 8.8	19.4 ± 7.5	18.2 ± 7.7	21.3 ± 11.7	0.27
Type of bowel preparation (%) [†]Standard [‡]Extended	 92 8	 92 8	 91 9	 84 16	0.45
Fasting blood glucose (mmol/L mean ± SD)	4.9 ± 0.4	5.9 ± 0.3 [a, c, d]	7.7 ± 2.5 [a]	8.5 ± 2.6 [a, e]	<0.001
Diabetes duration (years, mean ± SD)	Not relevant	Not relevant	11.8 ± 9.8	12.9 ± 7.6	0.54
HbA1c (%, mean ± SD) (mmol/mol)	Not relevant	Not relevant	7.3 ± 1.5 (56 ± 16)	7.7 ± 1.0 (61 ± 11)	0.068
Diabetes treatment (%) Diet alone SGLT2i Metformin Sulfonylurea DPP4 inhibitor Pioglitazone Acarbose	Not relevant	Not relevant	 9 3[§] 75 25 17 0 1 9	 0 100[¶] 84 38 46 3 0 11	

GLP-1 agonist Insulin			21	16	
Ketones (mmol/L)	0.4 (0.2, 0.7)	0.3 (0.1, 0.4) [f, g]	0.3 (0.2, 0.6)	0.5 (0.2, 1.1)	0.001

[a] p<0.001 vs normoglycaemia population, [b] p<0.05 vs SGLT2i-treated diabetes, [c] p<0.001 vs non-SGLT2i-treated diabetes, [d] p<0.001 vs SGLT2i-treated diabetes, [e] p<0.05 vs non-SGLT2i-treated diabetes, [f] p<0.01 vs normoglycaemia population, [g] p<0.01 vs SGLT2i-treated diabetes.

*Time since last consumption of any food or carbohydrate-containing liquid. [†]Standard: Moviprep (Macrogol 3350, potassium chloride, sodium chloride, sodium sulphate, ascorbic acid; sodium ascorbate) or oral Picoprep (sodium picosulfate, magnesium oxide, citric acid) + Glycoprep (sodium chloride, potassium chloride, ascorbic acid, sodium sulphate, Macrogol 3350). [‡]Extended: standard and additionally either double the usual volume of Glycoprep or an extra five days of oral Movicol (Macrogol 3350 with electrolytes) or a rectal Fleet enema (sodium biphosphate and sodium phosphate) in the half hour before the colonoscopy. [§]Last SGLT2i dose more than 80h before colonoscopy, [¶]Last SGLT2i dose less than 80 h before colonoscopy; DPP4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1; SGLT2i; sodium-glucose co-transporter 2 inhibitor. Impaired Fasting Glycaemia: capillary glucose 5.6–6.9 mmol/L. Normoglycemia: capillary glucose < 5.5 mmol/L; Ketones: capillary beta-hydroxybutyrate

Table 2. **Univariate correlations with capillary ketone concentrations**

	Overall (n = 358)	**Normoglycemia (n = 151)**	**Impaired fasting glycaemia (n=65)**	**Type 2 diabetes (non-SGLT2i) (n = 105)**	**Type 2 diabetes (with SGLT2i) (n = 37)**
Fasting duration	0.20 (0.10, 0.30)***	0.20 (0.04, 0.35)*	0.28 (0.03, 0.49)*	0.26 (0.07, 0.43)**	-0.02 (-0.34, 0.31)
Fasting glucose	-0.14 (-0.24, -0.04)**	-0.31 (-0.45, -0.15)***	0.14 (-0.11, 0.37)	-0.06 (-0.25, 0.13)	-0.32 (-0.59, 0.02)
Age	0.12 (0.01, 0.22)*	0.19 (0.03, 0.34)*	0.21 (-0.04, 0.44)	0.08 (-0.12, 0.26)	0.14 (-0.20, 0.44)
BMI	-0.22 (-0.32, -	-0.20 (-0.35, -	-0.07 (-0.31,	-0.24 (-0.42, -	-0.43 (-0.67,-

	0.12)***	0.04)*	0.18)	0.05) *	0.11)**
Time since last SGLT2i dose	NA	NA	NA	NA	-0.33 (-0.60, 0.00)*

Spearman correlation coefficient (95% CI) * p<0.05, ** p<0.01, *** p<0.001

Normoglycaemia: capillary glucose < 5.5 mmol/L and no history of diabetes; Impaired fasting glycaemia: capillary glucose 5.6 – 6.9 mmol/L and no history of diabetes; Type 2 diabetes (non-SGLT2i): not usually treated with SGLT2i (n=102) or if usually SGLT2i-treated, last SGLT2i dose > 80 hours before colonoscopy (n=3); Type 2 diabetes (with SGLT2i): last SGLT2i dose <80 hours before colonoscopy. SGLT2i: sodium-glucose co-transporter2 inhibitor; NA: Not Applicable

Table 3. **Multiple regression analysis of capillary ketone concentrations in SGLT2i-treated participants with diabetes**

Variable	**Beta coefficient**	**P Value**
Age	-0.086 (-0.39, 0.22)	0.57
Fasting duration	0.076 (-0.21, 0.37)	0.62
Fasting glucose	-0.17 (-0.47, 0.15)	0.29
Body Mass Index	-0.45 (-0.76, -0.14)	0.006
Time since last SGLT2i dose	-0.25 (-0.55, 0.07)	0.11

SGLT2i: Sodium glucose co-transporter 2 inhibitor

SGLT2i-treated participants: last SGLT2i dose taken < 80 hours before colonoscopy

Table 4. **Multiple regression analysis of capillary ketone concentrations in all study participants**

Variable	**Beta coefficient**	**P value**
Normoglycaemia v Impaired Fasting Glycaemia	-0.13 (-0.24, -0.02)	0.027
Normoglycaemia v Type 2 diabetes (non-SGLT2i)	-0.013 (-0.16, 0.13)	0.86
Normoglycaemia v Type 2 diabetes (with SGLT2i)	0.26 (0.14, 0.39)	< 0.001
Age	0.14 (0.04, 0.29)	0.010
Fasting duration	0.095 (0.000, 0.19)	0.059
Fasting glucose	-0.15 (-0.28, -0.02)	0.025
Body Mass Index	-0.23 (-0.32, -0.13)	< 0.001

Normoglycaemia: capillary glucose < 5.5 mmol/L and no history of diabetes; Impaired fasting glycaemia: capillary glucose 5.6 – 6.9 mmol/L and no history of diabetes; Type 2 diabetes (non-SGLT2i): not usually treated with SGLT2i (n=102) or if usually SGLT2i-treated, last SGLT2i dose > 80 hours before colonoscopy (n=3); Type 2 diabetes (with SGLT2i): last SGLT2i dose <80 hours before colonoscopy. SGLT2i: sodium-glucose co-transporter2 inhibitor.