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Efficacy and safety of continuous glucose monitoring on glycaemic control in patients with chronic pancreatitis and insulin-treated diabetes: A randomised, open-label, crossover trial

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Abstract

Aims: Continuous glucose monitoring (CGM) improves glycaemic control and reduces hypoglycaemia in type 1 and 2 diabetes, but its role in managing diabetes in chronic pancreatitis is unknown. We aimed to investigate the effect of CGM compared to self-monitoring of blood glucose (SMBG) on hypoglycaemia and glycaemic control in patients with chronic pancreatitis and insulin-treated diabetes.

Materials and Methods: In a randomised, open-label, crossover trial, 30 participants with chronic pancreatitis and insulin-treated diabetes were randomised to 50 days of CGM or SMBG, separated by a 20-day washout period. The primary endpoint was time in level 2 hypoglycaemia (<3.0 mmol/L). Secondary endpoints included additional CGM metrics, HbA1c, daily insulin dose, questionnaires, and safety outcomes.

Results: Twenty-nine participants completed the trial (mean age 64.4 ± 8.8 years; 22 men [75.9%]). There was a numerical reduction in time spent in level 2 hypoglycaemia with CGM compared to SMBG (mean difference −0.36%, 95% confidence interval (CI) −0.78% to 0.06%; $p = 0.09$). CGM improved time in range (3.9–10.0 mmol/L;

Filip Krag Knop and Morten Hasselstrøm Jensen currently employed by Novo Nordisk; the present work was performed independent of Novo Nordisk.

mean difference 7.46%, 95% CI 1.67% to 13.25%; $p = 0.01$), reduced time above range (>10.0 mmol/L; mean difference −6.55%, 95% CI −12.59% to −0.51%; $p = 0.04$), and reduced time below range (<3.9 mmol/L; mean difference −0.91%, 95% CI −1.79% to −0.03%; $p = 0.04$) compared to SMBG. No differences were observed for the safety endpoints.

Conclusions: In patients with chronic pancreatitis and insulin-treated diabetes, CGM increased time in range and reduced time above and below range. These findings highlight the potential of CGM in improving glycaemic control.

KEYWORDS

chronic pancreatitis, continuous glucose monitoring, glycaemic control, hypoglycaemia, secondary diabetes

1 | INTRODUCTION

Diabetes is one of the most common complications of chronic pancreatitis, and it carries an increased risk of severe hypoglycaemia.[1–7] This heightened risk arises from the unique and complex pathophysiology of diabetes in chronic pancreatitis, which differs substantially from both type 1 and 2 diabetes[7–9] In chronic pancreatitis, diabetes is not only characterised by beta cell loss and impaired insulin secretion but also by the loss of other islet cell hormones, such as glucagon. Additionally, exocrine pancreatic dysfunction contributes to nutrient maldigestion and impaired incretin hormone response, both of which play significant roles in blood glucose regulation.[10,11] Together, these elements make diabetes in chronic pancreatitis particularly challenging to manage, requiring early insulin therapy and placing patients at a higher risk of hypoglycaemia compared to type 2 diabetes.[2–6,12]

Self-monitoring of blood glucose (SMBG) has been a cornerstone in managing insulin-treated diabetes.[13,14] However, its intermittent readings offer only snapshots, making it challenging to capture real-time fluctuations and trends in glucose levels. These challenges underscore the need for advanced glycaemic monitoring strategies that provide continuous, real-time data. Continuous glucose monitoring (CGM) has improved glycaemic control and reduced hypoglycaemia in type 1 and 2 diabetes, driven by its glucose alerts and trend information that enable timely adjustments in insulin dosing or nutrient intake.[15–17] Its effectiveness has also been demonstrated in older adults with longstanding type 1 diabetes, a population at increased risk of hypoglycaemia, as patients with diabetes secondary to chronic pancreatitis, underscoring CGM's potential utility for the management of these patients.[18] Despite these advantages, there is a lack of data on the effects of CGM in patients with chronic pancreatitis and diabetes. This gap leaves clinicians with limited guidance on the role of CGM in this complex and challenging diabetes subtype.

We conducted a randomised, open-label, crossover trial to evaluate the efficacy and safety of CGM compared to SMBG in patients with chronic pancreatitis and insulin-treated diabetes. We hypothesised that CGM would lower the risk of hypoglycaemia and improve glycaemic control. The primary aim of this study was to evaluate the effects of CGM compared with SMBG on time spent in level 2 hypoglycaemia. Secondary aims included examining differences in additional CGM metrics, insulin dose, Haemoglobin A1c (HbA1c), and patient-reported outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This study was an investigator-initiated, randomised, open-label, crossover trial designed to investigate the effect of CGM compared to SMBG on glycaemic control in patients with chronic pancreatitis and insulin-treated diabetes. The study was conducted at the Centre for Pancreatic Diseases, Department of Gastroenterology and Hepatology, Aalborg University Hospital in Denmark from September 2022 to June 2024. The study protocol and its amendments were approved by The North Denmark Region Committee on Health Research Ethics (N-20210064). This research adhered to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent before enrolment. The study is registered at ClinicalTrial.gov (NCT05550480).

2.2 | Participants

Inclusion criteria were adult (≥18 years) patients with a definite diagnosis of chronic pancreatitis and insulin-treated diabetes based on the World Health Organization criteria for diabetes.[19,20] A definite diagnosis of chronic pancreatitis was established by one or more of the following M-ANNHEIM criteria: Pancreatic calcifications, moderate or marked ductal lesions, marked and persistent exocrine insufficiency, or characteristic histological findings.[19] Exclusion criteria included a history or suspicion of abdominal malignancies, acute pancreatitis requiring hospitalisation within the last four weeks, use of glucocorticoid medications in the preceding four weeks (except for inhaled glucocorticoids prescribed for chronic respiratory conditions), diabetes

onset before age 18, prior pancreatic, gastric, or vagotomy surgery, autoimmune pancreatitis, and current CGM use.

2.3 | Procedures

Patients meeting the eligibility criteria were randomly assigned in a 1:1 ratio using a computer-generated allocation sequence (block size of 6) to either 50 ± 2 days of CGM followed by SMBG or vice versa. Assignment to interventions was automatically handled by REDCap®. Each study period began with 20 ± 2 days of masked CGM, serving as baseline and washout periods. Masked CGM refers to the configuration in which the glucose concentrations recorded by the CGM were not visible to the participant, and the device did not trigger alarms in the case of hypoglycaemia or hyperglycaemia. During the final 20 ± 2 days of the SMBG period, patients also wore a masked CGM to facilitate the comparison of CGM-based endpoints across the two study periods. An outline of the study design is illustrated in Figure S1.

Participants were provided with a CGM system (Dexcom G6; Dexcom, San Diego, CA), measuring real-time glucose concentrations (2.2–22.2 mmol/L) at five-minute intervals. During the CGM period, all CGM devices were set to alarm if glucose levels fell below 3.9 mmol/L and to provide a warning if glucose was predicted to drop to 3.1 mmol/L within the preceding 20 min. Participants received comprehensive instructions on CGM use per manufacturer guidelines. During the baseline, washout, and SMBG periods, participants were instructed to monitor blood glucose levels according to their usual practices. Participants also maintained an insulin diary, recording daily basal and bolus doses.

Participants attended seven study visits to download CGM data and mask/unmask it as needed. At baseline, clinical and demographic data were collected from medical records and patient interviews. Previous or current alcohol abuse was defined as individuals who, either previously or at the time of inclusion, consumed more than 10 units of alcohol per week. Comorbidities were assessed using the Charlson Comorbidity Index (CCI) score and categorised as a score of 1–2 or >2.[21] Chronic pancreatitis aetiology was determined by the treating physician.[22] Blood samples were taken for biochemical analysis, including fasting C-peptide, and faecal elastase testing (<100 μg/g indicated insufficiency) was used to assess exocrine pancreatic function. Participants with previous faecal elastase <10 μg/g or recent testing had existing data used; others underwent a new test.

2.4 | Questionnaires

At baseline, and at the start and end of Study Periods 1 and 2, participants completed two questionnaires. First, the Clarke Hypoglycaemia Awareness Survey evaluates hypoglycaemia awareness in individuals with insulin-dependent diabetes. The eight-item survey covers symptoms and episodes of moderate to severe hypoglycaemia, with scores ranging from 0 to 1. A total score ≥4 indicates impaired awareness, classifying participants as hypoglycaemia-unaware (score ≥4) or aware (score <4).[23] Second, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was used to assess quality of life.[24] It includes five functional scales (physical, role, emotional, cognitive, social), three symptom scales (pain, fatigue, nausea/vomiting), a global health status scale, and single items on additional symptoms (dyspnoea, insomnia, appetite loss, constipation, diarrhoea) and financial impact. This study focused on the five functional scales and the global health status scale.

At the end of both study periods, participants completed the Patient Global Impression of Change (PGIC), a 7-point scale assessing perceived improvement, from 'very much worse' to 'very much improved'. Participants were classified as responders (minimal improvement) or non-responders (no change or worsening).[25]

2.5 | Endpoints

CGM-based endpoints were derived from the last 20 days of each study period, comparing CGM metrics between the CGM and SMBG periods. The primary endpoint was the difference in the percentage of time spent in level 2 hypoglycaemia (<3.0 mmol/L). Secondary endpoints included the following CGM metrics: Differences in time in range (3.9–10.0 mmol/L), time below range (<3.9 mmol/L), time in level 1 hypoglycaemia (3.0-3.8 mmol/L), time above range (>10.0 mmol/L), time in level 1 hyperglycaemia (10.1-13.9 mmol/L), time in level 2 hyperglycaemia (>13.9 mmol/L), and mean glucose. Additionally, the differences in the number of hypoglycaemic episodes (glucose <3.9 mmol/L lasting ≥15 minutes) and the total duration of hypoglycaemic episodes were estimated.[26] Proportions of patients achieving >50% time in range (3.9–10.0 mmol/L) and <1% time below range (<3.9 mmol/L) were also assessed between the CGM and SMBG periods, as per consensus CGM recommendations.[27] Glycaemic variability was assessed using the coefficient of variation (CV), standard deviation (SD), mean amplitude of glycaemic excursions (MAGE), and continuous overall net glycaemic action (CONGA) over 1- and 2-hour periods.[28]

Additional secondary outcome variables were the mean daily insulin dose during the last 20 days of each study period, HbA1c, quality of life (the five functional scales and the global health status scale from the EORTC QLQ-C30), improvement of health status (PGIC), and self-reported hypoglycaemia awareness (Clarke hypoglycaemia awareness survey), all assessed at the end of each study period. Finally, safety outcomes included device-related events and serious adverse events. Device-related events refer to any incidents linked to CGM use, while serious adverse events involve death, life-threatening situations, hospitalisation, or significant disability.

2.6 | Statistical analyses

The study was designed to detect a 50% reduction in the percentage of time spent in level 2 hypoglycaemia with the use of CGM versus

SMBG. The baseline percentage of time spent in level 2 hypoglycaemia was estimated to be 3%, with a standard error of 2.5%, based on data from studies involving older adults with longstanding type 1 diabetes.[18] This population was considered appropriate for reference due to their increased risk of hypoglycaemia, as comparable data for individuals with chronic pancreatitis and insulin-treated diabetes using CGM are limited. To achieve a statistical power of at least 80% with a two-sided type I error rate of 5%, a sample size of 24 participants was calculated. Considering an anticipated dropout rate of approximately 25%, the final target sample size was increased to 30 participants.

Data are presented as counts (%), means (SD), or medians (interquartile range [IQR]). For the primary endpoint analysis, time in level 2 hypoglycaemia in the last 20 days of each study period was compared using a linear mixed model. We incorporated the treatment regimen (CGM versus SMBG), treatment sequence, and study period as fixed effects, with patients nested within the sequence of study periods as a random effect.[29] The model estimate obtained was the mean difference between CGM and SMBG, reported with a 95% confidence interval (CI). The linear mixed model also checked for the presence of carry-over and period effects. Secondary outcomes were analysed using similar methods to the primary outcome. Categorical variables were evaluated using McNemar's test. The number and total duration of hypoglycaemic episodes were compared using the Wilcoxon signed-rank test. A modified intention-to-treat analysis was performed for the primary and CGM secondary endpoints, excluding one participant who withdrew before study procedures. For all other analyses, a complete case analysis approach was employed, excluding patients with missing data from the analyses. A two-sided *p*-value of less than 0.05 was considered statistically significant. All statistical analyses and data management were performed with SAS 9.4 (SAS Institute), Stata 17.0 (StataCorp), and R 4.3.2 (R Development Core Team).

3 | RESULTS

3.1 | Participants

From September 2022 to January 2024, 69 patients with chronic pancreatitis and insulin-treated diabetes were assessed for eligibility. Thirty were randomly assigned to the SMBG/CGM ($n = 15$) or CGM/SMBG ($n = 15$) groups, but one withdrew before treatment allocation, leaving 29 for analyses (Figure S2). The mean age of participants was 64 (SD, 8.8) years, with 22 (75.9%) being male. The mean duration of diabetes was 10 (SD, 8) years, and the median HbA1c was 59 mmol/L (IQR, 51–64). One participant had used a masked CGM in a previous trial, but none had used CGM for clinical reasons before this study. Baseline demographic and clinical characteristics of the cohort and the treatment sequence allocation groups are summarised in Table 1, with no significant differences between the groups. The median number of days with CGM measurements during the CGM period was 49 (IQR, 49–50), with 20 days (IQR, 19–20) in the final 20 days used in the analyses. In the SMBG period, the median was 20 days (IQR, 19–20) for masked CGM measurements.

3.2 | Glycaemic control endpoints

The results of the glycaemic control endpoints are detailed in Table 2 and Figure 1. We observed a numerical reduction in time spent in level 2 hypoglycaemia with CGM compared to SMBG (mean difference −0.36%, 95% CI −0.78% to 0.06%; $p = 0.09$) (primary endpoint). Additionally, secondary endpoints related to glycaemic control showed improvements. Time in range (3.9–10.0 mmol/L) was higher with CGM compared to SMBG (mean difference 7.46%, 95% CI 1.67–13.25; $p = 0.01$). Time below range (<3.9 mmol/L) was reduced (−0.91%, 95% CI −1.79 to −0.03; $p = 0.04$), as was time spent in level 1 hypoglycaemia (−0.55%, 95% CI −1.05 to −0.05; $p = 0.03$). Furthermore, time above range (>10.0 mmol/L; mean difference −6.55%, 95% CI −12.59 to −0.51; $p = 0.04$) and time in level 2 hyperglycaemia (>13.9 mmol/L; mean difference −4.61%, 95% CI −8.87 to −0.35; $p = 0.04$) were decreased with CGM. The number of hypoglycaemic episodes was lower with CGM (median 2, IQR 0–6) compared to SMBG (median 3, IQR 0–14) ($p = 0.02$). Additionally, the total duration of hypoglycaemic episodes was reduced with CGM (median 45 min, IQR 0–210) compared to SMBG (median 140 min, IQR 0–405) ($p = 0.01$). When considering the consensus CGM recommendations, 24 out of 29 patients (83%) had time below range (<3.9 mmol/L) <1% in the CGM period, compared to 19 out of 29 patients (66%) in the SMBG period (difference 17%, 95% CI −3% to 37%; $p = 0.06$). In addition, 25 out of 29 patients (86%) had time in range (3.9–10.0 mmol/L) >50% during the CGM period, compared to 17 out of 29 patients (59%) during the SMBG period (difference 27%, 95% CI 8%–47%; $p = 0.01$). There was also a reduction in CONGA2 during the CGM period (mean difference −0.10, 95% CI −0.20 to −0.01; $p = 0.04$), but no significant differences were observed in the remaining glycaemic variability metrics, mean glucose, HbA1c, or mean daily insulin dose between CGM and SMBG. For all endpoints, no significant carry-over or period effects were observed. Individual changes from baseline in time below range, time in range, and time above range during CGM and SMBG are presented in Figure S3.

3.3 | Questionnaire endpoints

The effects of CGM versus SMBG on quality of life (EORTC QLQ-C30) are reported in Table S1. Responses were missing for four patients. No significant differences between CGM and SMBG were observed.

For the PGIC, 7 out of 25 patients (28%) reported an improved health status after the CGM period, compared to 6 out of 25 patients (24%) after the SMBG period (difference 4%, 95% CI −23% to 31%; $p = 0.74$). PGIC responses were missing for four patients.

In terms of hypoglycaemia awareness, 24 out of 25 patients (96%) reported awareness after the CGM period, compared to 21 out of 25 patients (84%) after the SMBG period (difference 12%, 95% CI −5% to 29%; $p = 0.08$). Four patients did not complete the Clarke questionnaire.

TABLE 1 Demographic and clinical characteristics of chronic pancreatitis patients with insulin-treated diabetes, stratified by the treatment sequence.

	Total population ($n = 29$)	Sequence SMBG/CGM ($n = 15$)	Sequence CGM/SMBG ($n = 14$)
Demographic characteristics			
Age, mean (SD) years	64.4 (8.8)	64.5 (9.5)	64.2 (8.2)
Male sex, *n* (%)	22 (75.9)	11 (73.3)	11 (78.6)
Current smoking, *n* (%)	11 (37.9)	3 (20.0)	8 (57.1)
Previous or current alcohol abuse, *n* (%)	22 (75.9)	11 (73.3)	11 (78.6)
BMI, mean (SD) kg/m^2	23.9 (3.8)	23.6 (3.2)	24.3 (4.5)
Comorbidities			
CCI category, *n* (%)			
1–2	13 (44.8)	5 (33.3)	8 (57.1)
>2	16 (55.2)	10 (66.7)	6 (42.9)
Total Cholesterol, median (IQR) mmol/L	3.6 (3.2–4.9)	3.4 (3.1–4.9)	3.7 (3.2–4.3)
HDL, median (IQR) mmol/L	1.1 (0.9–1.5)	1.1 (0.9–1.6)	1.1 (1.0–1.5)
LDL, median (IQR) mmol/L[a]	1.9 (1.4–2.3)	1.6 (1.1–2.2)	2.1 (1.7–2.7)
Triglyceride, median (IQR) mmol/L	1.1 (0.9–1.6)	1.2 (0.9–2.1)	1.1 (0.9–1.3)
Chronic pancreatitis characteristics			
CP duration, mean (SD) years	9.9 (8.2)	11.5 (8.7)	8.2 (7.6)
CP aetiology, *n* (%)			
Alcohol abuse	18 (62.1)	9 (60.0)	9 (64.3)
Idiopathic	7 (24.1)	3 (20.0)	4 (28.6)
Post-necrotic	4 (13.8)	3 (20.0)	1 (7.1)
Enzyme replacement therapy, *n* (%)	25 (86.2)	13 (86.7)	12 (85.7)
Faecal elastase <100 μg/g, *n* (%)[a]	23 (82.1)	12 (80.0)	11 (84.6)
Diabetes characteristics			
Diabetes duration, mean (SD) years	10.1 (8.0)	10.3 (7.1)	9.9 (9.2)
HbA1c, median (IQR)			
In mmol/mol	59.0 (51.0–64.0)	59.0 (50.0–63.0)	58.0 (51.0–70.0)
In percentage	7.5 (6.8–8.0)	7.5 (6.7–7.9)	7.5 (6.8–8.6)
GAD65 autoantibodies >10 IU/L, *n* (%)[b]	3 (10.3)	2 (13.3)	1 (7.1)
Fasting C-peptide, median (IQR) pmol/L	252 (163–376)	183 (139–322)	268 (183–493)
Insulin treatment, *n* (%)			
Basal	14 (48.3)	9 (60.0)	5 (35.7)
Basal + bolus	15 (51.7)	6 (40.0)	9 (64.3)
Mean daily basal insulin dose, median (IQR) IE	16 (12–24)	16 (12–24)	16.0 (12–26)
Non-insulin therapy, *n* (%)	12 (41.4)	6 (40.0)	6 (42.9)
Biguanide, *n* (%)	10 (34.5)	4 (26.7)	6 (42.9)
SGLT2i, *n* (%)	3 (10.3)	2 (13.3)	1 (7.1)
DPP-4i, *n* (%)	1 (3.4)	1 (6.7)	0 (0.0)
GLP-1-RA, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes complications, *n* (%)	15 (51.7)	7 (46.7)	8 (57.1)
Retinopathy, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Nephropathy, *n* (%)	5 (17.2)	4 (26.7)	1 (7.1)
Neuropathy, *n* (%)	12 (41.4)	5 (33.3)	7 (50.0)
Macrovascular complications, *n* (%)	7 (24.1)	5 (33.3)	2 (14.3)
Clarke impaired hypoglycaemia awareness, *n* (%)	4 (13.8)	2 (13.3)	2 (14.3)

[a]Information on LDL and faecal elastase was missing for one patient.
[b]Information on GAD65 autoantibodies was missing for one patient.

TABLE 2 Effects of CGM versus SMBG on glycaemic control.

	Sequence	N	Treatment period 1	Treatment period 2	CGM versus SMBG (95% CI)	$P_{CGM\ versus\ SMBG}$	$P_{carry\text{-}over}$	P_{period}
Primary outcome								
Time in level 2 hypoglycaemia (<3.0 mmol/L), %	SMBG/CGM	15	0.52 ± 1.46	0.03 ± 0.03	−0.36 (−0.78 to 0.06)	0.09	0.66	0.52
	CGM/SMBG	14	0.07 ± 0.11	0.29 ± 0.50				
Secondary outcomes								
Time in range (3.9–10.0 mmol/L), %	SMBG/CGM	15	48.95 ± 19.17	56.7 ± 15.37	7.46 (1.67 to13.25)	0.01	0.32	0.91
	CGM/SMBG	14	63.34 ± 19.21	56.19 ± 24.66				
Time below range (<3.9 mmol/L), %	SMBG/CGM	15	1.61 ± 3.35	0.75 ± 1.26	−0.91 (−1.79 to −0.03)	0.04	0.99	0.91
	CGM/SMBG	14	0.69 ± 0.95	1.65 ± 2.01				
Time in level 1 hypoglycaemia (3.0–3.8 mmol/L), %	SMBG/CGM	15	1.08 ± 1.99	0.72 ± 1.24	−0.55 (−1.05 to −0.05)	0.03	0.86	0.45
	CGM/SMBG	14	0.62 ± 0.86	1.36 ± 1.54				
Time above range (>10.0 mmol/L), %	SMBG/CGM	15	49.44 ± 20.75	42.52 ± 16.30	−6.55 (−12.59 to −0.51)	0.04	0.34	0.90
	CGM/SMBG	14	35.97 ± 19.42	42.16 ± 25.81				
Time in level 1 hyperglycaemia (10.1-13.9 mmol/L), %	SMBG/CGM	15	31.36 ± 12.03	28.00 ± 8.95	−1.94 (−5.93 to 2.04)	0.33	0.33	0.47
	CGM/SMBG	14	26.10 ± 8.33	26.63 ± 11.98				
Time in level 2 hyperglycaemia (>13.9 mmol/L), %	SMBG/CGM	15	18.08 ± 14.76	14.52 ± 11.93	−4.61 (−8.87 to −0.35)	0.04	0.48	0.62
	CGM/SMBG	14	9.88 ± 12.71	15.53 ± 18.53				
Coefficient of variation, %	SMBG/CGM	15	32.32 ± 6.17	32.55 ± 6.08	−0.34 (−2.19 to 1.52)	0.71	0.31	0.54
	CGM/SMBG	14	30.06 ± 4.65	30.96 ± 5.16				
Standard deviation, mmol/L	SMBG/CGM	15	3.35 ± 0.82	3.22 ± 0.83	−0.18 (−0.44 to 0.07)	0.15	0.18	0.63
	CGM/SMBG	14	2.80 ± 0.55	3.05 ± 0.89				
MAGE, mmol/L	SMBG/CGM	15	8.02 ± 2.08	7.70 ± 2.00	−0.45 (−1.03 to 0.14)	0.13	0.09	0.66
	CGM/SMBG	14	6.42 ± 1.32	6.99 ± 2.11				
CONGA1, mmol/L	SMBG/CGM	15	1.45 ± 0.27	1.39 ± 0.27	−0.05 (−0.11 to 0.01)	0.13	0.13	0.67
	CGM/SMBG	14	1.24 ± 0.29	1.28 ± 0.33				
CONGA2, mmol/L	SMBG/CGM	15	2.06 ± 0.46	1.94 ± 0.41	−0.10 (−0.20 to −0.01)	0.04	0.14	0.69
	CGM/SMBG	14	1.72 ± 0.40	1.80 ± 0.45				
Mean glucose, mmol/L	SMBG/CGM	15	10.42 ± 1.98	9.88 ± 1.52	−0.52 (−1.08 to 0.04)	0.07	0.43	0.94
	CGM/SMBG	14	9.36 ± 1.59	9.86 ± 2.52				
HbA1c, mmol/mol	SMBG/CGM	15	57.80 ± 10.31	57.73 ± 9.19	−0.87 (−3.57 to 1.84)	0.52	0.64	0.55
	CGM/SMBG	12	55.33 ± 7.60	57.00 ± 9.59				
HbA1c, %	SMBG/CGM	15	7.44 ± 0.94	7.43 ± 0.84	−0.08 (−0.33 to 0.17)	0.52	0.64	0.55
	CGM/SMBG	12	7.21 ± 0.70	7.37 ± 0.88				
Mean daily insulin dose, IU	SMBG/CGM	15	27.59 ± 25.21	26.73 ± 24.02	−1.83 (−3.70 to 0.02)	0.05	0.48	0.29
	CGM/SMBG	12	32.79 ± 26.45	35.61 ± 26.95				

Note: *P* carry-over refers to the p-value testing the lasting effect of treatment between periods, while *P* period refers to the *p*-value testing differences between study periods.

Abbreviations: CGM, continuous glucose monitoring; CONGA, continuous overall net glycaemic action (assessed over 1 and 2 hours); HbA1c, haemoglobin A1c; MAGE, mean amplitude of glycaemic excursions; SMBG, self-monitoring of blood glucose.

3.4 | Safety

Four patients reported in total five episodes of local discomfort, redness, or mild bleeding during sensor application, with symptoms resolving immediately after sensor removal. No serious device-related adverse events were noted. There were no deaths or admissions with acute diabetes-related complications during the trial. Six participants reported 12 severe adverse events that led to hospitalisation. Among these, six hospitalisations were attributed to chronic pancreatitis, one to infection, three to hyponatraemia,

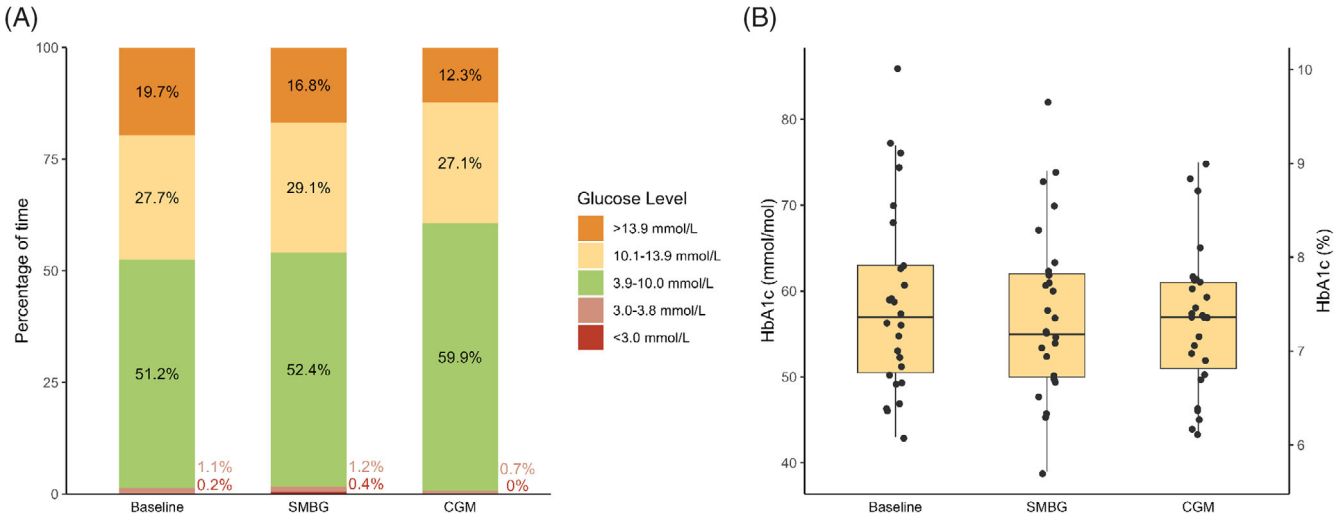

FIGURE 1 Glucose metrics at baseline, the self-monitoring of blood glucose (SMBG) period, and the continuous glucose monitoring (CGM) period. (A) The percentage of time spent at different glucose levels, as measured using CGM, during the baseline period, the SMBG period, and the CGM period. (B) Haemoglobin A1c (HbA1c) levels at baseline and after the SMBG and CGM periods, with individual HbA1c levels shown as dots. Two participants had missing values in either the SMBG or CGM period and are not included in plot B.

one to alcohol withdrawal treatment, and one related to percutaneous coronary intervention.

4 | DISCUSSION

This is the first randomised controlled trial to examine the effects of CGM versus SMBG in patients with chronic pancreatitis and insulin-treated diabetes. We found that the use of CGM, compared to SMBG, did not change the time spent with level 2 hypoglycaemia (primary endpoint). Nonetheless, using CGM led to an overall improvement in glycaemic control, with increased time in range, reduced time above range, and small reductions in time below range and glycaemic variability. No differences were found in daily insulin dose, HbA1c, or patient-reported outcomes between CGM and SMBG. Half of the patients were treated with basal insulin alone, while the other half received both basal and bolus insulin.

Hypoglycaemia is a significant concern in diabetes management, particularly for patients with chronic pancreatitis and diabetes who face an elevated risk of severe hypoglycaemia.[2–5] CGM has been shown in randomised trials of type 1 and type 2 diabetes to reduce time with hypoglycaemia.[15–18,29] In this study, we observed a numerical reduction in level 2 hypoglycaemia (albeit statistically insignificant) and reductions in both level 1 hypoglycaemia and overall glucose levels below 3.9 mmol/L. Additionally, CGM numerically increased the proportion of patients with time below range of less than 1%, in line with recommendations for this patient group,[27] while also significantly reducing both the number of and total duration of hypoglycaemic episodes. The effectiveness of CGM for reducing hypoglycaemia has also been demonstrated in older adults with longstanding type 1 diabetes, a population at increased risk of hypoglycaemia, and similarities to our study population.[18] Similar benefits have also been observed in other high-risk groups, such as individuals with impaired hypoglycaemia awareness.[29] A potential explanation for the lack of definitive proof of reduced level 2 hypoglycaemia in our study lies in the low occurrence of hypoglycaemia in our study population, particularly level 2 hypoglycaemia, which accounted for only around 0.5%. This may have limited our ability to detect a significant reduction with CGM and highlights that the risk of hypoglycaemia in patients with chronic pancreatitis and diabetes may be lower or more variable than expected. Despite high incidences of hypoglycaemia-associated hospitalisations in population-based studies (an epidemiological surrogate endpoint for severe hypoglycaemia),[2,3] other clinical cohort studies have similarly reported low frequencies of hypoglycaemia in patients with chronic pancreatitis and diabetes.[30,31] Several factors may explain this divergence between population-based and clinical studies. Participants may have experienced hypoglycaemia earlier, but later improved diabetes control or maintained higher glucose levels, either through improved management or fear of hypoglycaemia. Assessing fear of hypoglycaemia through a questionnaire could have further clarified the understanding of this low degree of hypoglycaemia. Additionally, 50% of participants did not use bolus insulin, which could have contributed to a lower risk of hypoglycaemia. Furthermore, most participants did not have hypoglycaemia unawareness, limiting CGM's ability to reduce time in level 2 hypoglycaemia, since participants were already able to detect and respond to symptoms of hypoglycaemia. This could also explain why CGM did not improve hypoglycaemia awareness.[32] Nonetheless, the reduction in overall time below range with CGM, along with more patients achieving less than 1% time below range and reduction in number and length of hypoglycaemic episodes, supports the potential benefits of CGM for reducing hypoglycaemia in patients with diabetes secondary to chronic pancreatitis.

As observed in previous randomised clinical trials in type 1 and 2 diabetes, we demonstrated a significant effect of CGM on

improving time in range and reducing time above range. Time in range was 7.5% higher with CGM compared to SMBG, a substantial difference, as a 5% improvement is considered clinically relevant.[26] We observed a 6.5% reduction in time above range with CGM, which aligns with previous studies that found a clear correlation between time in range and time above range.[33] Additionally, CGM increased the proportion of patients achieving more than 50% time in range by 27%. These improvements suggest CGM as a valuable tool for enhancing glycaemic control in patients with chronic pancreatitis and insulin-treated diabetes, reducing hyperglycaemia and the risk of long-term diabetes-related complications. Although no effect was observed on HbA1c, likely due to the study's short duration, a longer follow-up might reveal significant changes. Additionally, HbA1c may be a less reliable marker of glycaemic control in patients with chronic pancreatitis due to malnutrition and anaemia affecting its accuracy.[34,35]

Diabetes in chronic pancreatitis has often been characterised as 'brittle diabetes' due to frequent and significant glucose fluctuations.[8] Therefore, improving glucose variability, which is closely related to the risk of hypoglycaemia, is particularly important in this population.[36,37] However, contrary to studies in type 1 and 2 diabetes, we only observed marginal effects of CGM on glycaemic variability. In fact, our cohort exhibited less variability than expected, with a CV below 36%. This finding is in alignment with a previous observational cohort study by Lee et al., which also did not find increased glycaemic variability in patients with pancreatic diabetes.[30] This suggests that many patients with chronic pancreatitis may not have the high glycaemic variability once assumed, which could explain the lack of CGM effects on variability metrics. Further research is needed to assess CGM's role in populations with greater variability.

Evaluating treatment and monitoring efficacy should include the patient's perspective, with quality of life and improvements in health status as key measures. While some studies show improvements in quality of life with CGM, others, including this one, found no effect.[15,18] Several factors may explain this. First, the quality of life in chronic pancreatitis is significantly reduced, even compared to other chronic conditions, such as diabetes.[38] Hence, diabetes may not be the primary driver of reduced quality of life in these patients. Instead, the high burden of comorbidities, including pain and psychiatric comorbidities, may overshadow the potential benefits of improved diabetes management.[39] Additionally, short-term effects of CGM may be limited if hypoglycaemia, the most disruptive symptom, is absent. Improvements in quality of life may require more extended follow-up periods, as the long-term benefits of glycaemic control, such as reduced risk of diabetes-related complications, take time to manifest. Additionally, other studies often assess diabetes-specific outcomes, such as fear of hypoglycaemia, diabetes treatment satisfaction, and hypoglycaemic confidence.[15,18] Including these measures could have offered insights more directly related to diabetes, reducing the confounding effects of chronic pancreatitis and its comorbidities.

This study has several strengths. First, it is the first randomised controlled trial investigating the effect of CGM versus SMBG in patients with chronic pancreatitis and insulin-treated diabetes, offering high-quality evidence. Second, the crossover design is a key strength, as it allows each participant to serve as their own control, minimising between-subject variability and increasing statistical power. Third, the study achieved a high retention rate and demonstrated strong adherence to CGM, enhancing the reliability of the findings and indicating that CGM is feasible in this population. Fourth, we included a well-defined population of patients with definite chronic pancreatitis and insulin-treated diabetes, with few exclusion criteria, enhancing the generalisability of the findings and supporting the potential for future implementation in outpatient clinics. However, there are also limitations to consider. First, the sample size was relatively small. Additionally, while the crossover design is a strength, it introduces complexities, though no carry-over or period effects were observed, and dropout bias was minimised as all participants who started the study completed it. Another limitation is the low time spent in hypoglycaemia, which, in addition to the factors previously mentioned, may also be influenced by the 'healthy volunteer effect', potentially limiting generalisability. In addition, the heterogeneity of the patient population regarding glucose-lowering treatment represents a limitation. Approximately 50% of participants were on basal insulin alone, while 40% were also treated with non-insulin therapies. This variation may have influenced the impact of CGM on glycaemic control and hypoglycaemia, with potential differences in effects depending on the insulin regimen. Future studies could benefit from stratifying participants by insulin regimen to better understand how these therapies affect CGM outcomes in patients with chronic pancreatitis and diabetes. Finally, the short intervention duration limits assessment of the long-term effects of CGM use.

In conclusion, the use of CGM in patients with chronic pancreatitis and insulin-treated diabetes did not improve time spent in level 2 hypoglycaemia. However, CGM increased time in range and reduced both times above and below range, highlighting its potential to enhance glycaemic control in this unique diabetes subtype.

AUTHOR CONTRIBUTIONS

S.S.O., M.H.J., P.V., and A.M.D. designed the study. L.D. conducted the study. L.D. and P.B.S. acquired data. S.L.C. and L.D. managed data. S.S.O. and L.D. analysed data. S.S.O., L.D., M.H.J., S.L.C., and F.K.K. interpreted results. S.S.O. and L.D. drafted the manuscript, with all authors reviewing and approving the final version. S.S.O. and L.D. are guarantors, ensuring data integrity and analysis accuracy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Available upon reasonable request from the corresponding author.

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