

Original Article

Continuous glucose monitoring added to a standardised insulin protocol following total pancreatectomy

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ABSTRACT

INTRODUCTION. After total pancreatectomy (TP), patients are at high risk of hypoglycaemia regardless of insulin treatment modality. Information on treatment targets and modalities of insulin treatment following TP is sparse. This descriptive study presented experiences with a standardised insulin protocol and examined how the addition of intermittently scanned continuous glucose monitoring (isCGM) influenced the treatment of diabetes following TP.

METHODS. Results from two retrospective cohorts of patients who had undergone total pancreatectomy were collected, 30 patients not using isCGM served as references (operated in 2018-2019, mean age 65.4 years) for 40 patients using isCGM (operated in 2020-2021, mean age 63.3 years). An identical insulin treatment protocol was used for both cohorts. HbA_{1c}, insulin doses, weight and episodes with severe hypoglycaemia were recorded at three, six, nine and 12 months after TP. Percentage of time below range (TBR), time in range (TIR) and time above range (TAR) were collected for isCGM users.

RESULTS. HbA_{1c} and insulin doses were similar in the two groups during the first year following TP. In isCGM users, TBR was 0%, TIR 43-48% and TAR 52-57%. Episodes of severe hypoglycaemia were numerically but not significantly lower in isCGM users (zero versus four, $p = 0.21$). The same applied to days of readmittance 4.0 ± 7.7 days versus 15.5 ± 40 ($p = 0.13$) per patient/year.

CONCLUSIONS. In the first year following TP, the use of isCGM was not associated with better glycaemic control. A non-significant trend towards less severe cases of hypoglycaemia and a nonsignificant numerical reduction in days of hospitalisation were observed in isCGM users.

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Following total pancreatectomy (TP), the patient is 100% dependent on insulin treatment [1]. Diabetes that develops secondary to exocrine pancreatic disease, including TP, is classified as type 3c diabetes [2]. The concurrent loss of both insulin and glucagon secretion leads to brittle diabetes [3], characterised by an increased risk of both hypo- and hyperglycaemia [4].

TP is indicated in locally advanced or centrally located suspected pancreatic neoplasms, provided the

preoperational assessment is that TP would allow complete tumour resection. In Denmark, with six million inhabitants, the annual number of new cases of pancreatic cancer is approximately 1,000. [5]. Pancreatic surgery is centralised in four centres, of which Copenhagen University Hospital is the biggest, with an annual average of 250 pancreatic operations, including approximately 40 TPs.

The literature on treatment targets and modalities of insulin treatment in patients with diabetes following TP is sparse. A single-centre study from China based on 86 patients presented limited information and only reported glucose values and insulin dosages recorded during the first month after operation [6]. In a British single-centre study including 43 patients, data from the first 12 months following TP were analysed. Reported HbA_{1c} levels were around 65 mmol/mol at three months and 78 mmol/mol at 12 months. Information on insulin dosing was not available [7].

In earlier work, we described our experience with patients after TP, where treatment during the initial two post-operative weeks consisted of rapid-acting insulin administered with parenteral nutrition, along with basal insulin administered twice daily. According to this protocol, patients were gradually changed to enteral nutrition with rapid insulin administered as an injection before the three meals, but still with basal insulin given twice daily [8]. We have used this insulin protocol for several years.

The use of continuous glucose monitoring (CGM) in patients with type 1 diabetes is associated with a reduced risk of both hypo- and hyperglycaemia [9, 10]. Since 2020, Danish patients have routinely been offered intermittently scanned CGM (isCGM) following TP.

This retrospective study aimed to report our experiences with the insulin protocol and to assess the impact of adding isCGM hereto in the treatment of diabetes following TP.

Methods

Study design

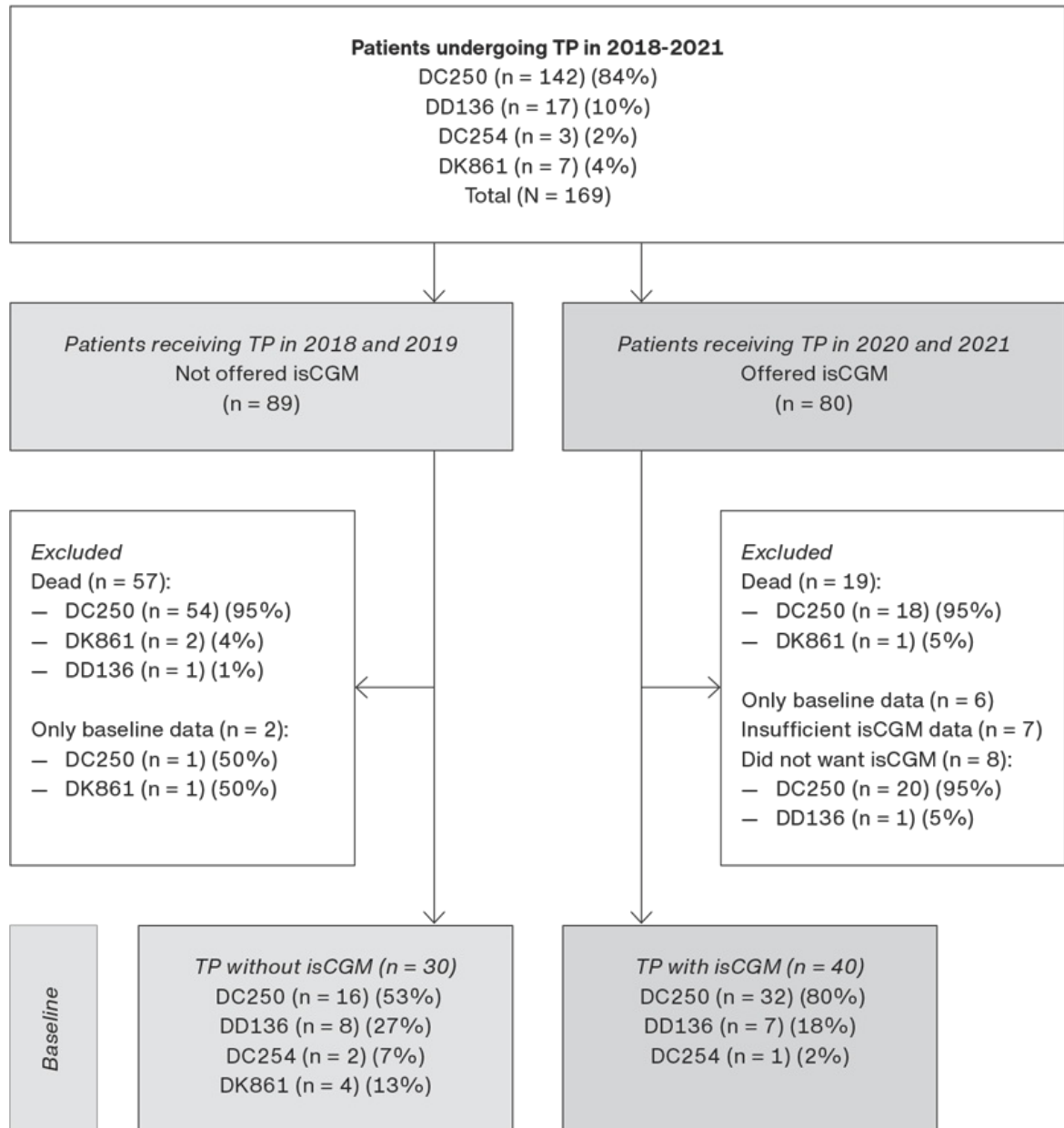
This retrospective study adopted a descriptive approach with systematic data collection of clinical data in two patient groups. After TP, each group followed the same insulin protocol during the first post-operative year. To assess the effect of isCGM, data were compared between a reference group of patients not using CGM and a group using isCGM. Data were collected in January 2022.

Study population

Patients who underwent TP at Copenhagen University Hospital, Rigshospitalet, from 2018 to 2021 were, in principle, eligible for inclusion in the study.

In Denmark, it is prohibited to obtain data from deceased persons without permission; consequently, only patients alive at the time of data collection could be included. Moreover, we excluded patients registered only with baseline data who did not want an isCGM or with insufficient isCGM data (**Figure 1**).

FIGURE 1 Patient selection flow chart.



DC250 = adenocarcinoma; DC254 = neuroendocrine tumour; DD136 = benign tumour; DK861: chronic pancreatitis; isCGM = intermittently scanned continuous glucose monitoring; TP = total pancreatectomy.

Using these criteria, it was possible to identify two patient groups. A total of 30 patients undergoing TP in 2018 and 2019, who used finger-prick for determination of blood glucose served as the reference group (the -isCGM cohort) for 40 patients undergoing TP in 2020 and 2021 and who initiated isCGM shortly before hospital discharge (the +isCGM cohort). In the period from 1 January 2020 to 31 March 2021, the patients used Libre 1 isCGM (Abbott), which is without alarms. Thereafter, they used Libre 2, where the alarms for hypoglycaemia were set at 4.0 and 15 mmol/l. The change from Libre 1 to 2 was motivated by the presence of the alarm function and initiated when Libre 2 became available in our hospital. The operative procedures used in the two groups were identical.

Diabetes management

In hospital management: An insulin treatment algorithm has previously been developed to minimize the risk of hypoglycemia and was used in all patients prior to discharge [10]. During the first 16 hours after TP, patients received a glucose infusion (50 g/100 ml) at 10 ml/hour together with an intravenous infusion of rapid-acting insulin aspart at 1.5 IU per hour.

On the second post-operative day, a continuous infusion of parenteral nutrition (Kabiven) was initiated according to weight, e.g. body weight 70 kg: 9,240 kJ with insulin aspart 0.2 IE/g glucose. This treatment was continued until sufficient oral intake was achieved. Simultaneously, basal insulin (insulin detemir) 0.2 IU/kg/day was initiated in two equal doses at 8 am and 6 pm. The aim for premeal BG levels was 5-10 mmol/l. In case of a BG exceeding the target prior to a main meal, subcutaneous supplemental insulin aspart was administered according to the following sliding scale: BG 10-14 mmol/l: 1 IU; 14-18 mmol/l: 2 IU; > 18 mmol/l: 3 IU.

The patients were gradually initiated on oral feeding. The aim was intake of a minimum of 150 g of carbohydrates per day, typically as 40 g at the three main meals and 10-20 g as snacks three times daily. Two units of insulin aspart were administered before each main meal. The patients in both cohorts were educated concerning diabetes, including carbohydrate counting, by a team of specialised nurses, who attended the patients three times weekly during hospitalisation. An insulin-to-carbohydrate ratio of 20, corresponding to 1 IU of insulin aspart per 20 g of consumed carbohydrates, was recommended to all patients.

After discharge, basal insulin (insulin detemir) 0.2 IU/kg/day was administered at 8 am and 6 pm, along with insulin aspart before the three main meals. Insulin treatment was adjusted by phone contact or regular outpatient visits. Patients using isCGM were recommended to scan the device before each meal and before going to sleep. The BG goal in both cohorts was 5-10 mmol/l before meals. Patients in the reference group were recommended to measure their glucose at least four times daily.

Treatment targets were HbA_{1c} 7.7-8.6% (60-70 mmol/mol) corresponding to a time in range (TIR) of 3.9-10.0 mmol/l > 50% and a time below range of (TBR) < 3.9 mmol/l ≤ 1% of the time. isCGM data were recorded and uploaded to Libre View (Abbott).

Data collection

Baseline

Baseline data included the patient's age, date of recruitment (defined as the date of TP), height and weight before TP, history with diabetes before TP, adjuvant oncological treatment, pathologic diagnosis and International Classification of Diseases, tenth version (ICD-10) code, weight before operation and at discharge, and dosage of basal and mealtime insulin at discharge.

Follow-up at three, six, nine and 12 months

Follow-up data included information on ongoing oncologic treatment, HbA_{1c}, daily doses of basal and mealtime insulin, number of insulin administrations and episodes of severe hypoglycaemia since the previous follow-up. Severe hypoglycaemia was defined as patient-reported events requiring hospital admission within the past three months. At 12 months: the total number of days admitted to any hospital in the 12 months following discharge after the operation was calculated.

Libre View data at three, six, nine and 12 months

From the Libre View database, data were recorded regarding the previous 14 days as follows: mean glucose, TIR 3.9-9.9 mmol/l, time above range (TAR) > 9.9 mmol/l and TBR < 3.9 mmol/l.

Statistical analysis

Statistical analyses included descriptive statistics. Data are presented as mean $\pm$ standard deviation (SD) and percentage. Differences between groups were analysed by unpaired t-test or Welch's test if the distribution was non-parametric. The level of significance was two-sided, $p < 0.05$. SPSS (IBM SPSS Statistics) version 26 was used.

Trial registration: not relevant. In accordance with Danish regulations for quality improvement projects, this study was approved by the Hospital Management at the Centre for Cancer and Organ Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark.

Results

From January 2018 to December 2019, a total of 89 patients underwent TP. Among these, 30 were alive and were followed at our clinic. These were included as a reference group.

A total of 80 patients underwent TP between January 2020 and December 2021. During this period, 19 patients died. In another 21 patients, data were insufficient or the patient did not want isCGM. Thus, 40 isCGM users were included (Figure 1).

The two cohorts were similar in age, sex distribution and weight both before and immediately after TP (**Table 1**). There were fewer with a cancer diagnosis in the reference group (53%) than in the groups using isCGM (80%).

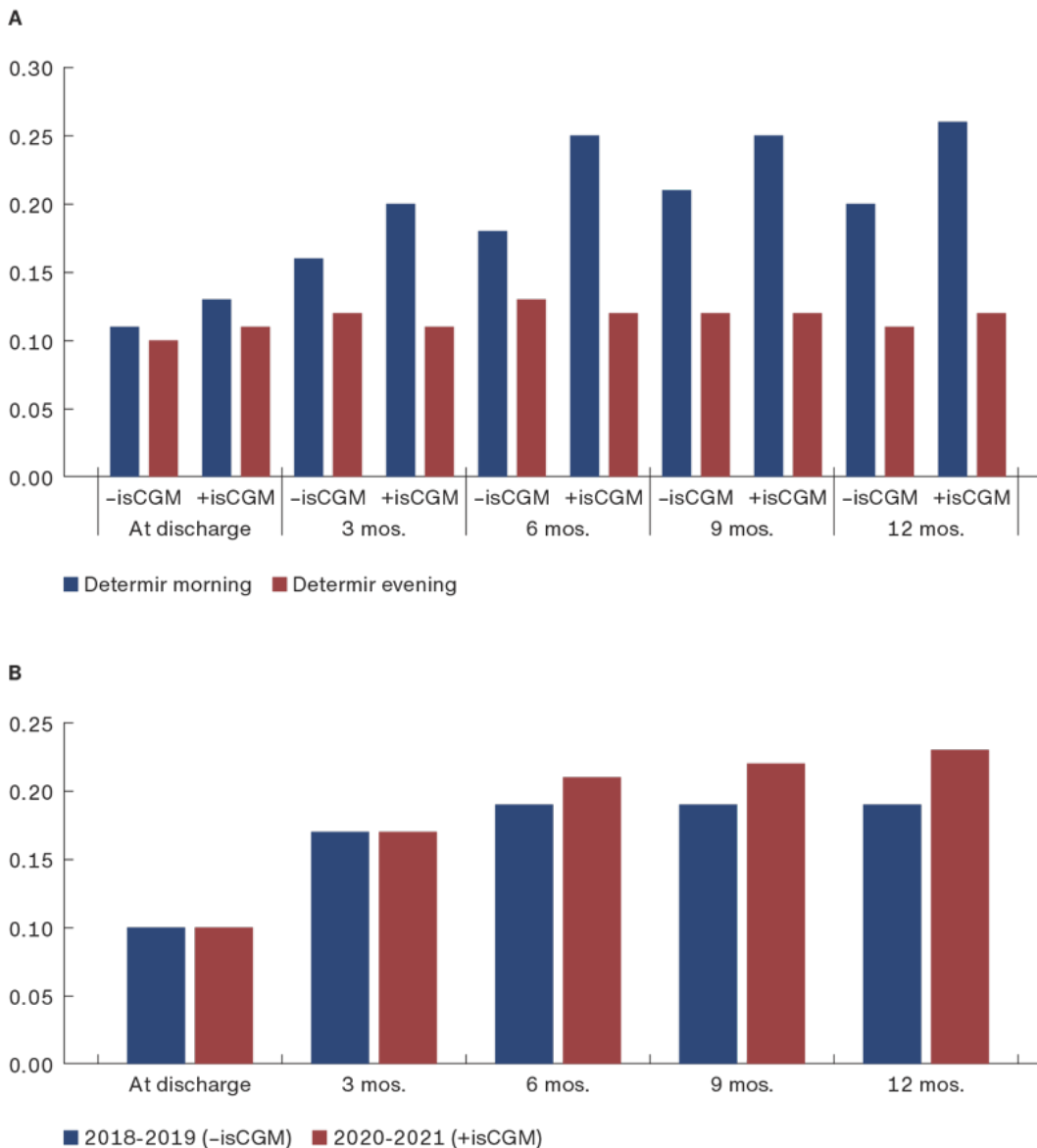
TABLE 1 Baseline characteristics of patients following total pancreatectomy and subsequently either not using intermittently scanned continuous glucose monitoring (reference) or using it.

	2018-2019: without isCGM (N₋ = 30)	2020-2021: with isCGM (N₊ = 40)	p value
Age, mean $\pm$ SD, yrs	63.3 $\pm$ 9.1	65.4 $\pm$ 10.6	0.370
Sex, n (%)			
Male	14 (47)	24 (60)	
Female	16 (53)	16 (40)	
Weight, mean $\pm$ SD, kg			
Before total pancreatectomy	74.0 $\pm$ 15.1	76.6 $\pm$ 16.9	0.521
At discharge	73.7 $\pm$ 14.8	73.9 $\pm$ 16.7	0.961
BMI, mean $\pm$ SD, kg/m ²			
Before total pancreatectomy	24.7 $\pm$ 4.2	25.6 $\pm$ 4.3	0.389
At discharge	24.6 $\pm$ 4.0	24.7 $\pm$ 4.6	0.895
Preoperative diabetes, n (%)			
Type 1 diabetes	2	2	
Type 2 diabetes	6	10	
Subtotal	8 (27)	12 (30)	

isCGM = intermittently scanned continuous glucose monitoring;
SD = standard deviation.

The total dosages of basal insulin detemir increased from 0.2 IU/kg/day (95% confidence interval (CI): 0.09-0.32 IU/kg/day) at discharge to 0.4 IU/kg/day (95% CI: 0.28-0.63 IU/kg/day) at 12 months, mainly due to an increase in the morning dosage, with no differences between the two groups (**Figure 2 A**).

FIGURE 2 A. Basal insulin (IU/kg/day) divided into morning and evening dosages in 30 patients not using intermittently scanned continuous glucose monitoring (–isCGM) and 40 patients using isCGM (+isCGM) at discharge following total pancreatectomy and, 3, 6, 9 and 12 months after operation. **B.** Total dosages of mealtime insulin (IU/day/kg) in 30 patients not using isCGM (–isCGM) and 40 patients using isCGM (+isCGM) at discharge following total pancreatectomy and three, six, nine, and 12 months after the operation.



Dosages of total daily mealtime insulin per kg increased in both groups from an average of 0.1 IU/kg/day at discharge to 0.2 IU/kg/day after 12 months. There were no differences between the two groups (Figure 2 B).

Three months after discharge, HbA_{1c} was $7.9 \pm 1.1\%$ (62 ± 12 mmol/mol) in the reference group and $8.1 \pm 1.0\%$ (65 ± 11 mmol/mol) in isCGM users. After 12 months, the corresponding values were $8.6 \pm 1.2\%$ (70 ± 14 mmol/mol) and 8.5 ± 1.0 (69 ± 11 mmol/mol).

Among isCGM users, the device was actively used more than 90% of the time. TBR was 0% throughout the observation period, and TIR remained stable between in the 43-58% range.

Four cases of severe hypoglycaemia leading to hospital admission were recorded in the reference group. Among the isCGM users, no cases of severe hypoglycaemia leading to hospital admission were recorded. These numbers are not statistically significant (zero versus four in four individual patients, $p = 0.21$).

At discharge, the mean weight was 68.8 ± 11.7 kg in the reference group and 68.3 ± 10.5 kg among isCGM users, with no significant between-group difference. At 12 months, the corresponding values were 67.3 ± 17.4 kg and 71.5 ± 15.5 kg ($p = 0.26$).

The number of days spent in hospital after discharge from TP and until 12 months after TP was 15.5 ± 39.6 in the reference group and 4.0 ± 7.7 among isCGM users ($p = 0.13$).

Discussion

The present study showed that in the 12 months following TP, the insulin algorithm used in both groups resulted in similar HbA_{1c} levels. The observations in the group using CGM showed that 50-60% of the patients reached the glycaemic goal (HbA_{1c}: 60-70 mmol/mol) and that TBR was zero. Recording of cases of severe hypoglycaemia and days of hospitalisation suggests that use of CGM may reduce both. However, as these observations are nonsignificant, further substantiation is required.

The motivation for using insulin detemir as basal insulin was that this group of patients was expected to require less basal insulin during the night than during the day because the liver glycogen depots were expected to be low due to insufficient and unstable carbohydrate intake [10]. This approach seems to be warranted. The dosages of insulin detemir increased by 70-80% during the 12 months, and this increase was mainly rooted in an increase in the morning insulin dosage (Figure 2 A).

As mentioned, the literature on insulin treatment protocols in TP outpatients is sparse. In studies reporting on insulin treatment and the corresponding effect of glycaemic control [4, 6, 7], no or very few details regarding the specific insulin regimens are given. Two studies from Japan and Great Britain reported the HbA_{1c} in the 12 months following TP to be 63 and 78 mmol/mol, respectively. Severe hypoglycaemia was described in 18% and 20% of the patients, respectively [5, 6].

In the present study, we report four cases of hypoglycaemia requiring hospitalisation, all from the reference group of patients not using isCGM during the first post-operative year.

In our study, the use of isCGM did not lead to improved metabolic control as assessed by HbA_{1c}. However, hospitalisations due to severe hypoglycaemia were seen in patients using isCGM. The goal of TBR was set to 1%, and this goal was reached as TBR was 0 in the isCGM users throughout the 12-month study period. Thus, isCGM users were able to avoid severe hypoglycaemia with subsequent hospitalisation or extended hospital stay. A recent observational study, which compared ten patients with diabetes for 4-6 years following TP to matched type 1 diabetes patients, reported a TBR of 2.3% versus 4.5%, respectively [11].

Study strengths and limitations

The strength of this study is detailed information on insulin treatment and corresponding HbA_{1c} values in patients after TP. The same insulin regimen was used throughout the study, and the use of isCGM allowed for detailed mapping of blood glucose levels throughout the observation period.

It is a clear limitation that the study was retrospective and not randomised. Moreover, the study only included patients who were alive at the time of data collection. This meant that approx. 60% of all the operated patients in the reference group were not included. Another limitation is that the results of glucose measurements in the reference group were unavailable. We were only able to report whether patients had been hospitalised for

severe hypoglycaemia or not. For the outcome of total hospital days during the first year after TP, data were restricted to absolute counts, which prevented more detailed analyses.

Conclusions

Based on an insulin regimen consisting of twice daily insulin detemir and mealtime insulin aspart in patients with diabetes after TP, the use of isCGM during the first post-operative year may result in a lower risk of severe hypoglycaemia and an HbA_{1c} almost identical to that of patients not using isCGM. In isCGM users, TBR < 3.9 mmol was 0% during the first years following TP. Moreover, a trend towards reduced days of readmission in isCGM users was observed.

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