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CASE REPORT

Offlabel use of Medtronic MiniMed 780G in the management of cystic fibrosis related diabetes in people requiring insulin total daily doses below 8 units: encouraging data from our population

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Abstract
Cystic fibrosis (CF)-related diabetes (CFRD), characterized by partial to complete impaired insulin secretion, is the most common extra-pulmonary complication of CF. Actually, insulin is the only approved therapy for its management. Advanced hybrid closed loop (AHCL) systems are the gold standard therapy for type 1 diabetes and have been proposed for other insulin-dependent forms of diabetes, including CFRD. With AHCL systems, people with CFRD can better manage several typical disease-related issues, such as minimal insulin requirements, its variability due to exacerbations or concomitant steroid therapies, nutritional behaviors, the co-existence of CF complications as intestinal malabsorption or liver disease. SmartGuard, the AHCL system for Medtronic Minimed 780G, requires a minimum of 8 units per day to operate. In this paper, we expose a case of two young women with CFRD with total daily insulin requirements < 8 UI, using off-label SmartGuard system over a 3 years of follow-up period, suggesting an evaluation of its use also in people with minimal insulin needs, considering its beneficial impact in glucose control and quality of life.

Keywords Cystic fibrosis related diabetes · Insulin pumps · Advanced hybrid closed loop

Introduction

Cystic fibrosis (CF)-related diabetes (CFRD) is the most common extra-pulmonary complication of CF, occurring in 2% of children, 19% of adolescents, and 40–50% of adults [1]. CFRD is characterized by impaired insulin secretion, but its pathogenesis is still not fully clarified. Several factors contribute to insulin deficiency in individuals with CFRD, as pancreatic fibrosis and alterations in cystic fibrosis transmembrane conductance regulator (CFTR -, which has a direct role in physiological insulin secretion). Furthermore, CFRD-related liver disease and the frequent use of steroid therapies can worsen glucose metabolism in this population.

Actually, insulin is the only approved therapy for CFRD and its early introduction plays a well demonstrated positive impact on nutritional status and lung function in this population. However, CFRD management is characterized by several critical peculiarities, only partially solvable with a multiple daily injection (MDI) scheme (i.e. minimal insulin total daily doses, variability in insulin requirements due to exacerbations or concomitant steroid therapies, need for frequent meals during the day, possible concomitant CF related complications as intestinal malabsorption or liver disease). Insulin pumps with advanced hybrid closed loop (AHCL) systems are actually considered the gold standard therapy for type 1 diabetes and other insulin-dependent forms of diabetes [2]. In the last years, moreover, several studies were published on the use of insulin pumps, with or without AHCL systems, for CFRD management, providing increasing evidence to be considered the most appropriate therapy in this population [3, 4].

Currently, 4 AHCL systems are available in Italy: SmartGuard (for MiniMed 780G/Guardian4) Control-IQ (for Tandem T-slim/Dexcom G6), Diabeloop (for Roche Accu-check

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Insight/Dexcom G6) and CamAps (for Mylife Ypsopump/Dexcom G6).

Among them, SmartGuard system is based on a combination of parameters derived from a proportional integral derivative algorithm and a predictive adaptation algorithm, to adjust the insulin dose in response to blood glucose values. SmartGuard requires a minimum of 8 units and a maximum of 250 units per day to operate [5].

195 individuals with CFRD are actually followed at the Endocrinology Unit of Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico of Milan, Italy. 45 of them actually use an insulin pump. Among 18 individuals using SmartGuard and, 2 people show a total daily insulin requirement < 8 UI.

In this paper, we report the clinical characteristics and the advantages obtained with the off-label use of the SmartGuard system, which was proposed to them due to their peculiar clinical characteristics.

Data displayed in this case report are from our registry on patients with CFRD currently followed at our Clinic. The research protocol was approved by the Ethics Committee of the IRCCS Ca' Granda – Ospedale Maggiore Policlinico Foundation (study number 4166, ID 89,006) and has been registered on ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04379726). A written informed consent was provided by each participant.

Table 1 Epidemiological and clinical characteristics of case 1 and 2

	Case 1	Case 2
Age (years)	40	33
Sex	Female	Female
Ethnicity	Caucasian	Caucasian
Genetics	F508del/F508del	F508del/F508del
Diabetes duration (years)	14	3
BMI (Kg/m^2)	18.4	22.9
Concomitant therapies	Acetylsalicylic acid 100 mg/day; Mycophenolate720 mg/day; Tacrolimus 1.5 mg/day; Prednisone 5 mg/day, Pancrelipasi 25,000 U; Pantoprazole 40 mg/day; Vitamin D 50,000 U/month	Pancrelipasi 10,000 U; Vitamin D 50,000 U/month Tiotropium bromide AR; Salbutamol AR; Doxyribonuclease AR; Elexa/teza/ivacaftor37,5/25/50 mg
Concomitant diseases	previous lung transplantation; previous kidney transplantation; previous intestinal occlusions; chronic kidney disease; osteoporosis; exocrine pancreatic insufficiency;	exocrine pancreatic insufficiency; chronic respiratory failure

Age and diabetes duration refer to the time of switch to Medtronic MiniMed 780G. BMI: body mass index; AR: as required

Epidemiological and clinical characteristics of Case 1 and 2 are reported in Table 1.

Case report

Case 1: female, 40 years

Patient nr.1 was diagnosed with CF at birth (F508del/F508del mutation) and underwent bilateral lung transplantation in 2009. Since then, she developed CFRD. In 2014, an MDI insulin scheme was started (Glargine 4 UI and Lispro 2 + 4 + 2 UI) and she was proposed to switch to flash glucose monitoring (FGM - Abbott Freestyle Libre 2). Furthermore, she participated in a structured educational program (training to FGM data interpretation, insulin therapy management and carbohydrates counting), structured in 4 face-to-face meetings and performed by a multidisciplinary staff (i.e. nutritionist, diabetologist and nurse). In 2016 she started hemodialysis due to end-stage renal disease (ESRD) and, in 2019, she underwent renal transplantation.

During hemodialysis, the patients experienced several critical issues in CFRD management, resulting in frequent hypoglycemic episodes.

For this reason, she was proposed to switch to an insulin pump with predictive low-glucose suspend system (PLGS-Medtronic MiniMed 640G). A basal infusion rate was set as follows: 0.10 U/h from 00.00 am to 08.00 am, 0.15 U/h from 08.00 am to 11.00 am, 0.10 U/h from 11.00 am to 3.00 pm, 0.05 U/h from 3.00 pm to 8.00 pm, 0.125 U/h from 8.00 pm to 12.00 pm. An Insulin/carbohydrates ratio (ICR) was set at 1/50 for breakfast, 1/15 for lunch and 1/50 U/gr for dinner (due to the concomitant therapy with prednisone 5 mg/day, her insulin needs at lunch and in the immediate after-lunch period were significantly higher than the rest of the day. We completely faced this issue reducing dramatically her I/CHO ratio at lunch). An insulin sensitivity factor (ISF) of 1/100 was set all day long. Since then, glucose variability significantly improved, with a reduction in hypoglycemic episodes frequency. Glycated hemoglobin levels (HbA1c) always remained below 53 mmol/mol (7%) and time in range (TIR) higher than 70%, average of total daily dose (TDD) of insulin was 7.6 UI (Fig. 1A), reaching only temporarily the minimal necessary total amount of insulin for the labeled use of SmartGuard.

Once the AHCL system became available, she was proposed to switched Medtronic MiniMed 780G with the aim to further improve her glucose variability and reduce the burden of diabetes management. The patient was explained about the offlabel use of SmartGuard when insulin requirements fell below 8 U/day and she signed the informed consent.

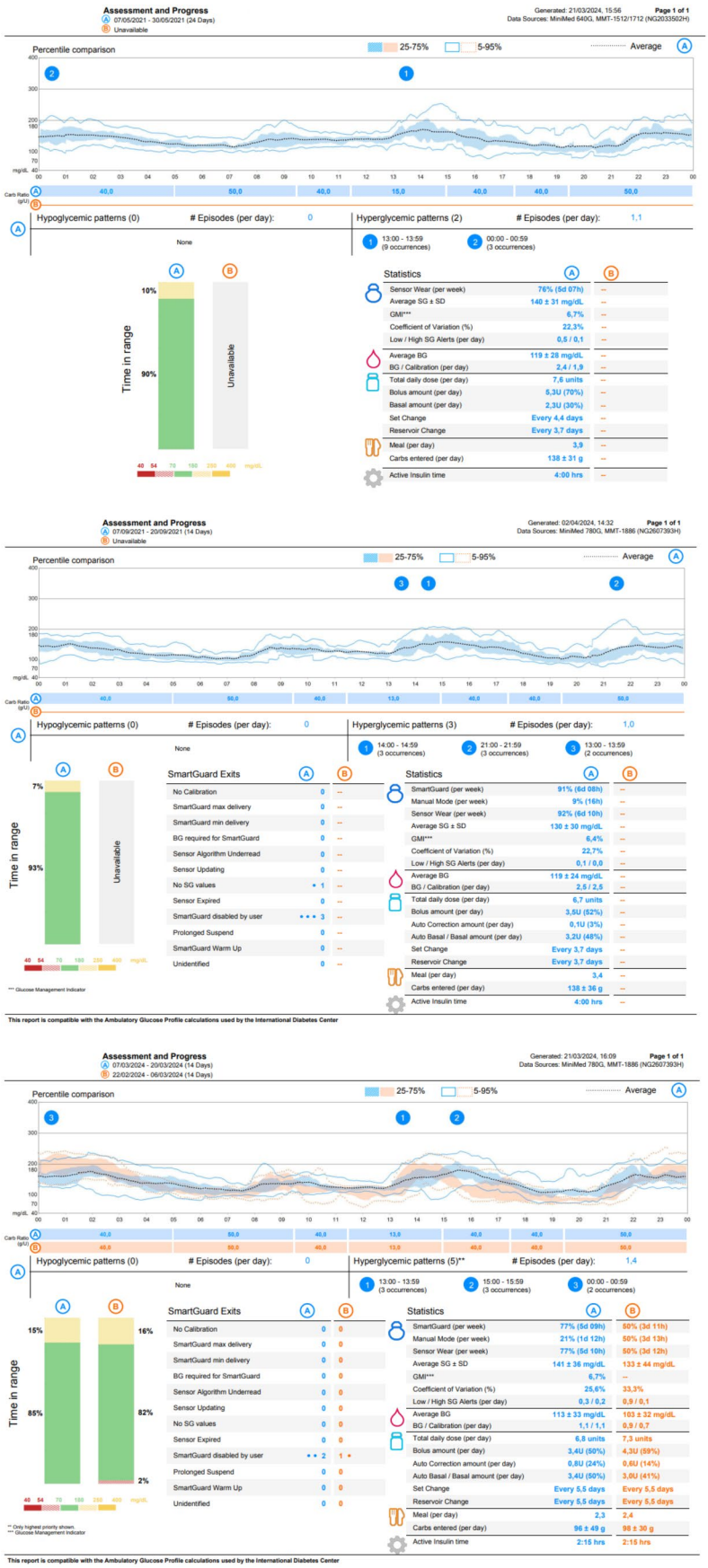

Fig. 1 Case 1: A- AGP from the last 14 days using Medtronic MiniMed 640G; B – 14 days-AGP from the first 14 days using Medtronic MiniMed 780G; C – 14 days-AGP 24 months after switching to SmatGuard (AGP: ambulatory glucose profiles, SG: sensor glucose; SD: standard deviation; GMI: glucose management indicator; BG: blood glucose)

Table 2 – Case 1: glucose control parameters, 14days - AGP metrics, insulin requirements, SmartGuard settings and questionnaires outputs before switching to Medtronic MiniMed 780G, 2 weeks after and at last FU visit

	Before switching to Minimed 780G	2-weeks after switching to Minimed 780G	Last follow up visit (24 months)
Glucose control parameters			
Glucose (mg/dl)	101	107	99
HbA1c (%)	6.1	6.0	6.3
14 days - AGP metrics			
AG (mg/dl)	140	130	141
SD (mg/dl)	31	30	36
CV	22.3	22.7	25.6
GMI (%)	6.7	6.4	6.7
TIR (%)	90	93	85
TAR (%)	10	7	15
TBR (%)	0	0	0
Insulin Requirements			
TDD (U)	7.6	6.7	6.8
Basal amount (U)	5.3	3.2	3.4
Auto Correction (U)	-	0.1	0.8
Bolus Amount (U)	2.3	3.5	3.4
SmartGuard settings			
AI (h)	-	2:30	2:30
Target	-	120	100
Questionnaires Outputs			
DTSQ total score	25	31	30
ADDQoL AWI score	-2.94	-0.78	-0.78

AG: average glucose; SD: standard deviation; CV: coefficient of variation; GMI: glucose management indicator; TIR: time in rang; TAR: time above range; TBR: time below range; AI: active insulin; DTSQ: Diabetes Treatment Satisfaction Questionnaire; ADDQoL: Audit of Diabetes Dependent Quality of Life; AWI: average weighted impact

Switching to Minimed 780G, ICRs and ISF remined unchanged, a glycemic target of 100 mg/dl and an active insulin time (AIT) of 2.30 h was set and SmartGuard system was activated. During the first two weeks, her average TDD was 7.5 UI. Her Ambulatory Glucose Profile (AGP) metrics always displayed an optimal glucose control, reaching the desired targets for the patient, as shown in Fig. 1B. Since then and at each following outpatient visits, data from the AGP always showed an optimal glucose control (Fig. 1C).

Furthermore, the patient reported a significant improvement in perceived treatment satisfaction and in quality of life, as routinely assessed with the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and e the Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaires.

Glucose control parameters, AGP data, insulin requirements, SmartGuard settings and questionnaires outputs are summarized in Table 2 for case 1.

Table 3 – Case 2: glucose control parameters, 14days - AGP metrics, insulin requirements, SmartGuard settings and questionnaires outputs switching to Medtronic MiniMed 780G but before using SmartGuard, 2 weeks after and at last FU visit

	Minimed 780G in Manual Mode	2-weeks after switching to SmartGuard	Last follow up visit (18 months) with SmartGuard
Glucose control parameters			
Glucose (mg/dl)	99	95	98
HbA1c (%)	6.3	5.9	6.0
14 days - AGP metrics			
AG (mg/dl)	119	123	142
SD (mg/dl)	39	33	40
CV	30.1	26.8	28.2
GMI (%)	6.2	6.3	6.7
TIR (%)	92	94	82
TAR (%)	7	6	18
TBR (%)	1	0	0
Insulin Requirements			
TDD (U)	14.3	5.7	5.4
Basal amount (U)	1.7	2.2	2.4
Auto Correction (U)	-	0.3	0.4
Bolus Amount (U)	12.6	3.5	3.0
SmartGuard settings			
AI (h)	-	2:30	2:30
Target	-	120	100
Questionnaires Outputs			
DTSQ total score	22	30	31
ADDQoL AWI score	-2.42	-0.89	-0.84

AG: average glucose; SD: standard deviation; CV: coefficient of variation; GMI: glucose management indicator; TIR: time in rang; TAR: time above range; TBR: time below range; AI: active insulin DTSQ: Diabetes Treatment Satisfaction Questionnaire; ADDQoL: Audit of Diabetes Dependent Quality of Life; AWI: average weighted impact

Case 2: female, 33 years

Patient nr.2 was diagnosed with CF at birth (F508del/F508del mutation). In 2020 she was diagnosed with CFRD and she started insulin therapy (Insulin Lispro 3 UI at lunch and 3 UI at dinner). Flash glucose monitoring was performed with a FGM system (Abbott Freestyle Libre 2). At outpatient visits, she always demonstrated an optimal glucose control, with HbA1c always below 53 mmol/mol (7%) and TIR always above the desired target (70%).

In 2021 she started Ivacaftor/Tezacaftor/Elexacaftor (ETI) therapy and, since then, she experienced a worsening of glucose profiles, with significant increase in time spent above range (TAR) and in insulin requirements at meals (Lispro 8 UI at lunch and 8 UI at dinner).

Given daily insulin requirements above 8 unites per day, she was proposed to switch from an MDI insulin scheme

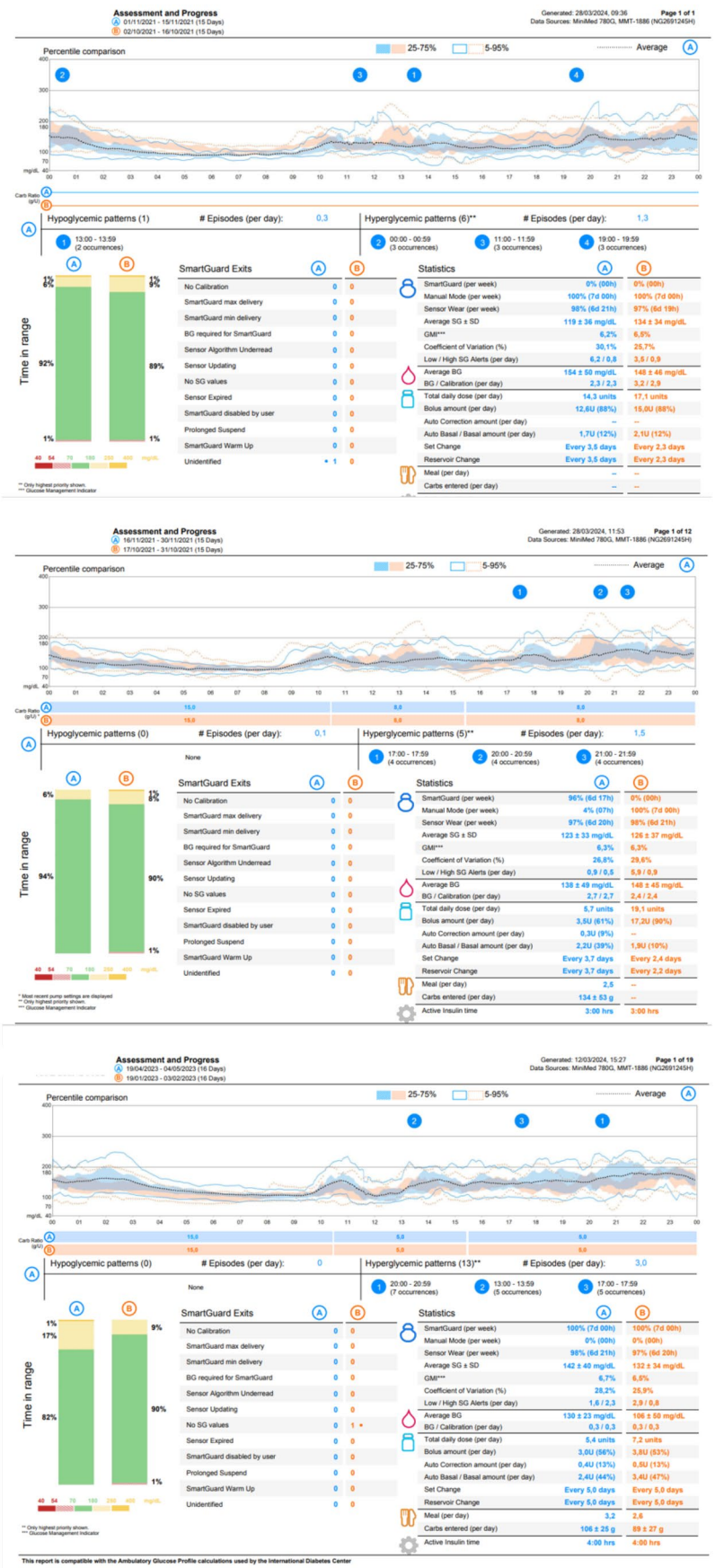

Fig. 2 case 2: A- AGP from the last 14 days with MiniMed 780G with Manual Mode; B - AGP with MiniMed 780G after 2 weeks with Auto Mode; C 14 days-AGP 18 months after switching to SmatGuard (AGP: ambulatory glucose profiles, SG: sensor glucose; SD: standard deviation; GMI: glucose management indicator; BG: blood glucose)

to insulin pump with AHCL system (Medtronic MiniMed 780G, SmartGuard algorithm), after attending a structured educational program on the use of this device. A basal insulin infusion rate was set at 0.1 U/h from 00.00 am to 12.00 pm, an ICR of 1:15 at breakfast, 1:8 at lunch and 1:8 at dinner and ISF of 1:60 were set. Glucose target and AIT were set, respectively, at 100 mg/dl and 3:00 h (Fig. 2A).

6 months after the beginning of ETI therapy, her insulin requirements decreased again and, at outpatient visits, the data downloaded from her device showed an average insulin TDD of 5.7 UI per day. TIR was 94%, her Coefficient of Variation (CV) was 26.8 and she had no hypoglycemic events (Fig. 2B). Again, she reported an improvement in quality of life and perceived satisfaction to the treatment, as assessed with DTSQ and ADDQoL questionnaires.

For all the reasons mentioned above, we agreed with the patient to continue with the AHCL system for the management of CFRD therapy, despite TDD below 8 UI per day. The patient was warned about the offlabel use of the system and signed the informed consent.

Since then, during periodic outpatient visits, HbA1c levels and AGP metrics always remained within the pre-established targets and average TDD below 8.0 UI/day (Fig. 2C).

Glucose control parameters, AGP data, insulin requirements, SmartGuard settings and questionnaires outputs are summarized in Table 3 for Case 2.

Discussion

As mentioned above, insulin pumps and, in particular, AHCL systems are gaining more and more evidence to be considered the gold standard treatment for CFRD [3]. Therefore, their use should be implemented in this population.

Actually, all AHCL systems can be considered to manage CFRD. Medtronic MiniMed 780G, working with AHCL system SmartGuard, is the only insulin pump with seven days-lasting infusion sets (instead of three days, as for other insulin pumps) and this feature is particularly appreciated by people with CFRD, being their complex polytherapy partly simplified.

Nevertheless, SmartGuard system is labeled only for people with diabetes requiring more than 8 U per day.

To our knowledge, no efficacy and safety data about the use of this system in patients with CFRD and insulin requirements below 8 units are currently available.

For case 1 and case 2, respectively, SmartGuard system was activated when TDD was only temporarily above 8 U or when TDD was steadily above 8 U, but significantly dropped after the first months receiving ETI. In both cases, after the automatic mode was set, data from the AGP always displayed an optimal glucose control, as shown in Figs. 1 and 2. Their TIR and CV always remained broadly within the desired target (> 70% and < 35, respectively).

All patients reported a significant improvement in quality of life and treatment satisfaction since SmartGuard was activated, due to the perceived decreased burden related to hypoglycaemic episodes and hyperglycaemia management.

These case reports could be a first tip for the use of SmartGuard in individuals with CFRD with daily insulin requirements below 8 U, considering its remarkable impact on diabetes management and people quality of life.

Author contributions V.G. and I.C. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. A.G.and V.R. collected data, carried out the initial analyses, and reviewed and revised the manuscript. V.G. and E.O. designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. V.G. 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.

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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