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Impact of blinded retrospective continuous glucose monitoring on clinical decision making and glycemic control in persons with type 2 diabetes on insulin therapy

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Abstract *Background and aims:* Blinded retrospective continuous glucose monitoring (rCGM) provides detailed information about real-life glycaemic profile. In persons with type 2 diabetes without adequate glycaemic control, the structured introduction of rCGM may be beneficial to sustain improvements in diabetes management.
Methods and results: 102 individuals with insulin-treated type 2 diabetes, age less than 66 years old and HbA1c >7.5%, were recruited. Participants performed a 7-day blinded rCGM (iPro2) every four months for one year. Biochemical, anthropometric, and rCGM data was collected. Participants' and healthcare professionals' perceptions were assessed.

90 participants completed the protocol. HbA1c was 9.1 ± 0.1% one year prior to enrolment and 9.4 ± 0.1% at enrolment ($p < 0.01$). With the rCGM-based intervention, a decrease in HbA1c was achieved at 4 months (8.4 ± 0.1%, $p < 0.0001$), and 12 months (8.1 ± 0.1%, $p < 0.0001$). A significant increase in time-in-range was observed (50.8 ± 2.4 at baseline vs 61.5 ± 2.2% at 12 months, for 70–180 mg/dL, $p < 0.001$), with no difference in exposure time to hypoglycaemia. After 12 months, there was an increase in self-reported diabetes treatment satisfaction ($p < 0.05$).
Conclusion: In persons with type 2 diabetes and poor metabolic control, specific data from blinded rCGM informed therapeutic changes and referral to targeted education consultations on nutrition and insulin administration technique. Therapeutic changes were made more frequently and targeted to changes in medication dose, timing, and/or type, as well as to lifestyle. Together, these brought significant improvements in clinical outcomes, effective shared decision-making, and satisfaction with treatment.
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Introduction

Type 2 diabetes remains today one of the most challenging public health problems globally. While considerable efforts have been made towards higher quality of care and support to empower persons with diabetes [1], still around half of people with type 2 diabetes currently fail to achieve an adequate glycaemic control [2,3], with an overwhelming majority simultaneously not achieving management goals for lipids and arterial pressure [3,4].

The pursuit of an adequate management of this heterogeneous disease depends greatly on the adherence to and efficacy of pharmacological options and the ability to monitor and adapt daily life habits [5]. Healthcare services increasingly adopt a person-centred approach, with the person as the focus of a multidisciplinary team, in which the chronic care model is the gold standard for diabetes clinical practice. Beyond that, diabetes management should evolve to fully integrate the input and preferences of the person [6]. Requirements of diabetes management frequently generate emotional and financial distress, in people with diabetes and non-professional caregivers alike, with frustration and burnout being expressed by healthcare professionals [7].

Shared goal setting is more than establishing a numerical target, as it depends on the behavioural change strategies employed [8]. The progress to a truly collaborative care interaction between people with diabetes and healthcare professionals requires acquisition of knowledge, competences, and communication skills, and then requires a wealth of information regarding daily habits and physiological reactions that are not easily available to both persons and healthcare professionals. Glycaemic control is usually evaluated through the quantification of blood glycated haemoglobin (HbA1c), indicating the average of exposure to glucose levels within the previous 2–3 months. Albeit useful to broadly follow the time between consultations, HbA1c has recognizable limitations as it is not able to provide indication on specific defects of glucose metabolism and is scantly able to provide specific actionable information for the fine tuning of therapeutic changes [9]. On the other hand, sporadic self-monitoring of capillary blood glucose (SMBG) provides limited information, and is not routinely performed in people with type 2 diabetes.

In recent years, advances in technology have facilitated the access to a more extensive picture of daily glycaemia profiles, namely through retrospective continuous glucose monitoring (rCGM) systems [10]. The main uses have been to evaluate overall glycaemic control and glycaemic patterns, detection of hypoglycaemia episodes, identification of glucose variability, and incorporation in lifestyle management and motivation support. Published meta-analyses have consistently pointed to a beneficial effect of introducing CGM on management of type 2 diabetes [11–13], although specific studies vary in methodology and results.

While standards of care mention that optimal use of CGM requires proper review and interpretation of the data by both people with diabetes and healthcare professionals to ensure that data are used in an effective and timely manner, most lack training on how to interpret and drive actionable information from CGM [14], and who constitute good candidates for benefit from CGM introduction in clinical practice needs to be established [15].

The main aims of the present study were to: i) evaluate the impact of therapeutic decisions informed by quadrimestral rCGM on glycaemic control in people with type 2 diabetes on insulin therapy, and ii) explore the attitudes and perceptions of people and healthcare professionals regarding rCGM use.

Methods

The study, designated as ADJUST, was conducted at the outpatient clinic of the Portuguese Diabetes Association (APDP), involving a multidisciplinary care team. This is a specialized diabetes care unit, where most users are referred to from primary care for education and/or intensive follow-up. Ethical and regulatory approvals were obtained from the local Ethics Committee at APDP (639/2015) and from the Portuguese Data Protection Authority (G003/2015). The study is registered as NCT04141111.

Selected candidates were persons with type 2 diabetes from both genders, 18–65 years of age, on a stable insulin dose for at least 60 days prior to inclusion, with HbA1c >7.5% in the previous 60 days, and able to adhere to protocol requirements. Exclusion criteria included current or planned pregnancy, use of any CGM device in the previous year, serious or unstable medical or psychological condition, and the inability to comply with study requirements. Invitation for enrolment was done by the care team, especially when discrepancies existed between HbA1c and glycaemic levels (for example, the log book not reflecting the laboratory HbA1c result to a clinically relevant degree) or particular bad control. Informed consent was obtained from all participants.

The ADJUST study comprised four evaluation moments, with a 7-day rCGM performed at every four months, for twelve months. The study's primary objective was to compare HbA1c before and after clinical decision on diabetes treatment based on rCGM. The study's secondary objectives were to compare before and during rCGM use: 1. The number of therapeutic regimen adjustments; 2. Frequency of self-measured blood glucose (SMBG) performed; 3. Therapeutic regimen adjustments (drug, dosage and duration); 4. Health status and treatment satisfaction; and 5. Determine people and healthcare professionals' attitudes and perceptions regarding rCGM use.

The study's primary endpoint was mean HbA1c level. The study's secondary endpoints were the number of SMBG values, number of therapy regimen adjustments, health status, and treatment satisfaction. The study also implemented a qualitative exploratory questionnaire, for participants and healthcare professionals.

Statistical analysis

Previous studies have shown that HbA1c biological variation in type 2 diabetes is around 1.7%. From this value, a

sample size of 100 participants was deemed sufficient for detecting differences of at least 0.67 percentage points on the primary variable with a power of 80% and a significance level of 95%, in a retrospective–prospective study.

Statistical analyses was performed using GraphPad 6 and SPSS 20. Parametric and non-parametric tests were used to compare variables between gender (t-test with independent samples or Mann–Whitney) and to compare variables along time (paired t-test and Wilcoxon test for 2 by 2 comparison, or ANOVA Friedman for 4 time points comparison), depending on confirmation of population normality (evaluated by the Kolmogorov–Smirnov test). All analysis were performed with a confidence interval of 95%. Findings were considered statistically significant when $p < 0.05$.

Study procedures

The following data was collected on the initial visit: sociodemographic, anthropometric and biochemical characterization, presence of co-morbidities and diabetes complications, treatment satisfaction using the DTSQS questionnaire, and mental health status using the GHQ-12. These questionnaires are evaluated with a GHQ score >24 indicating psychological distress, and a DTSQS partial score <23 indicating low satisfaction. Retrospective data was also collected in the initial visit, according to existing electronic health records for the previous 12 months: mean number of SMBG values per day, HbA1c and other glucose control laboratory measures, and therapeutic regimens. On months 4, 8 and 12, glycaemic control, therapeutic regimen adjustments, treatment satisfaction, and health status were evaluated.

On each visit, an iPro™2 rCGM device (MiniMed™ Medtronic) was placed. During each 7 days monitoring period, participants were asked to perform four SMBG measurements daily for calibration. Additionally, participants received a diary in order to register the type and timing of food intake, physical activity and medication, SMBG values, and diabetes-related events they might have experienced in the previous 4 months.

rCGM data was interpreted by a physician experienced in CGM interpretation and a report was delivered to the healthcare team within one week. This report was discussed together by the person and the healthcare team, either in consultation or by phone, agreeing on therapeutic changes. Hypoglycaemia episodes were defined as any continuous period below 54 mg/dL glucose. If necessary, extra consultations for nursing assistance, nutrition or education were scheduled, to address specific needs identified during rCGM review.

At study conclusion, both participants and healthcare team members were provided a questionnaire regarding experience with rCGM. These had a quantitative and a qualitative section. The quantitative questions were answered through a Likert scale, from 0 (strongly disagree) to 6 (strongly agree). For participants it included 3 dimensions: Study participation, device use, and impact on diabetes self-management. For professionals, it included 4 dimensions regarding rCGM use: Contribution to therapeutic decision, professional–patient relation, treatment adherence, and benefit to other type 2 diabetes participants. Both questionnaires were reviewed by a panel of experts prior to application.

Results

Study population

Recruitment for the ADJUST study was closed with 102 persons with type 2 diabetes on insulin therapy. 9 dropouts were registered (due to labour, travel, or health issues). An additional 3 participants were excluded from data analysis, for screen failure or inability to adhere to the protocol. Dropouts were not different in demographics or HbA1C from those that completed the study. Ninety participants completed the study.

Baseline characteristics for the participants that completed the ADJUST protocol are shown in Table 1. Differences among gender were limited to arterial pressure and waist circumference values which were higher in men. Additionally, metformin was the most common non-insulin treatment at study initiation (72%), either alone (46%) or combined with other hypoglycaemic agents (especially DPP4 inhibitors, 26%). Mixed insulin analogues (58%), long-acting insulin analogue (34%), and fast-acting

Table 1 Baseline characteristics of the participants included in the final analysis (n = 90).

	ADJUST cohort
Gender (%)	
Female	50
Male	50
Age (years)	57.5 ± 0.6
Duration of diabetes (years)	16.9 ± 0.8
HbA1c (%)	9.4 ± 0.1
Education level (%)	
Primary school	32
Preparatory school	11
Secondary school	41
University	16
Occupational status (%)	
Employed	53
Retired	31
Unemployed	16
Weight status (%)	
Normal	9
Overweight	35
Obese	56
Diabetes complications (%)	
Retinopathy	59
Peripheral vascular disease	40
Neuropathy	32
Nephropathy	17
Stroke	4
Comorbidities (%)	
Hypertension	86
Dyslipidemia	81
Obesity	56
Hypothyroidism	6
Clinical depression	6

Table 2 Characteristics from the retrospective and prospective study. Hypo episodes are considered as instances where CGM recorded values below 70 mg/dL glucose.

	−12 months	Baseline	4 months	8 months	12 months
Biochemical & Anthropometric					
HbA1c (%) (mmol/mol)	9.1 ± 0.1 (76)	9.4 ± 0.1 (79) ###	8.4 ± 0.1 (68) ***	8.4 ± 0.1 (68) ***	8.1 ± 0.1 (65) *** &
BMI		31.0 ± 0.5	31.2 ± 0.5	31.2 ± 0.5	31.1 ± 0.5
Waist circumference (cm)		102.2 ± 1.3	102.5 ± 1.3	102.9 ± 1.4	103.2 ± 1.3
rCGM parameters					
eHbA1c (%)		8.1 ± 0.1 §§§	7.8 ± 0.1 §§§	7.6 ± 0.1 §§§	7.5 ± 0.1 * §§§
TIR 70–140 mg/dL (%)		25.4 ± 1.8	30.3 ± 2.0	32.4 ± 1.9 *	32.6 ± 1.9 **
TIR 70–180 mg/dL (%)		50.8 ± 2.4	56.9 ± 2.5 *	59.8 ± 2.3 *	61.5 ± 2.2 ***
SD (mg/dL)		52.7 ± 1.8	51.4 ± 1.9	49.9 ± 1.7	48.5 ± 1.5 *
CV (%)		28.5 ± 0.8	28.9 ± 0.8	29.2 ± 0.8	28.6 ± 0.7
>140 mg/dL (%)		73.2 ± 2.0	68.4 ± 2.1	66.2 ± 2.0	66.1 ± 2.0 *
>180 mg/dL (%)		48.0 ± 2.5	42.0 ± 2.6	38.9 ± 2.3 *	37.3 ± 2.2 **
<70 mg/dL (%)		1.4 ± 0.3	1.2 ± 0.2	1.3 ± 0.2	1.0 ± 0.2
<54 mg/dL (%)		0.5 ± 0.2	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
Hypo episodes (n)		1.3 ± 0.3	1.2 ± 0.2	1.7 ± 0.3	1.4 ± 0.2
Nocturnal >140 mg/dL (%)		67.4 ± 2.9	61.0 ± 2.9	58.2 ± 2.8 **	60.2 ± 3.0 **
Nocturnal >180 mg/dL (%)		40.5 ± 3.1	33.6 ± 2.9	31.7 ± 2.9	32.3 ± 2.7
Nocturnal <70 mg/dL (%)		2.7 ± 0.7	2.5 ± 0.6	2.2 ± 0.5	1.4 ± 0.4
Nocturnal <54 mg/dL (%)		1.2 ± 0.4	0.7 ± 0.3	0.4 ± 0.1	0.4 ± 0.2
Nocturnal Hypo episodes (n)		0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1
Scales					
GHQ-12		13.6 ± 0.5	12.9 ± 0.5	13.4 ± 0.5	13.5 ± 0.5
DTSQ Satisfaction		27.4 ± 0.6	28.2 ± 0.6	28.3 ± 0.6	28.7 ± 0.5 *
DTSQ Hyper		4.3 ± 0.1	3.6 ± 0.1 **	3.4 ± 0.1 ***	3.3 ± 0.1 ***
DTSQ Hypo		1.2 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.5 ± 0.1

Abbreviations: eHbA1c (HbA1c estimated from CGM data), GHQ (Global Health Questionnaire), DTSQ (Diabetes Treatment Satisfaction Questionnaire). ###$p < 0.001$ vs −12 months; ***$p < 0.001$ vs baseline; **$p < 0.01$ vs baseline; *$p < 0.05$ vs baseline; & $p < 0.05$ vs 4 months; §§§$p < 0.001$ vs respective HbA1c.

insulin analogue (32%), followed as the most common drug classes found at the enrolment visit.

Overall, participants entered the study in good mental health, with a mean GHQ score of 13.6 ± 0.5. Only 3 participants scored positive for psychological distress. The DTSQS partial score for satisfaction showed that the participants were generally satisfied with current treatment at study initiation (27.4 ± 0.6). Fifteen participants registered low satisfaction. Regarding the DTSQ partial score for hypo- and hyperglycaemia, perceived frequency of hypoglycaemia was low, with an average score of 1.2 ± 0.1, while participants perceived a much higher frequency of hyperglycaemia, with an average score of 4.3 ± 0.1.

Retrospective data

The retrospective biochemical data available did not differ from that observed at study initiation, with the exception of HbA1c which was lower 12 months earlier (9.4 ± 0.1% at study initiation vs 9.1 ± 0.1% 12 months before, $p < 0.001$).

Participants performed 2.6 ± 0.1 SMBG measurements in the 12 months prior to the enrolment visit. In that period, nearly half of the participants (46%) reported performing a mean of three daily SMBG measurements, and 11% used more than three (up to five) strips daily. Medications used to treat diabetes during the year before entering the study were similar to those being actively taken at the time of the enrolment visits. In that period, changes in diabetes treatment, defined as starting, stopping, or changing the dose of a single medication, were relatively rare (22%). In total, there were 0.4 ± 0.2 changes per participant.

rCGM prospective intervention

HbA1c decreased throughout the intervention with rCGM, from 9.4 ± 0.1% at baseline to 8.4 ± 0.1% at 4 and 8 months ($p < 0.001$), and further to 8.1 ± 0.1% at 12 months ($p < 0.001$ vs baseline) (Table 2). Additionally, glucose variability decreased, as evaluated by standard deviation to mean glycaemia (from 52.7 ± 1.8 at baseline to 48.5 ± 1.5 mg/dl glucose at 12 months, $p < 0.05$). The coefficient of variation (CV) remained in acceptable terms (from 28.5 ± 0.8 at baseline to 28.6 ± 0.7% at 12 months), with no change due to lower mean blood glucose. Eighty-one percent of participants had a clinically relevant improvement (≥0.5%) of glycaemic control during the study. All other biochemical and anthropometric variables remained similar throughout the study.

The decrease observed in HbA1c was associated with an increased time in range (TIR) (Table 2). For 70–180 mg/dl, TIR increased from 50.8 ± 2.4% at baseline to 61.5 ± 2.2% at 12 months ($p < 0.001$). In addition, there was a decrease of time of exposure to hyperglycaemia (from 48.0 ± 2.5 to

37.3 ± 2.2% >180 mg/dL glucose, $p < 0.01$) and a trend to a decrease in the time of exposure to hypoglycaemia (from 0.5 ± 0.2 at baseline to 0.2 ± 0.1% at <54 mg/dL glucose). Frequency of hypoglycaemic episodes was similarly unchanged with rCGM (from 0.5 ± 0.2 at baseline to 0.3 ± 0.1 episodes weekly <54 mg/dL glucose at 12 months).

A decrease in nocturnal exposure to hyperglycaemia was also observed throughout the study (from 40.5 ± 3.1 at baseline to 32.3 ± 2.7% >180 mg/dL glucose at 12 months, $p < 0.05$) (Table 2). Nocturnal exposure to hypoglycaemia showed a decreased trend from baseline to 12 months (from 1.2 ± 0.4 at baseline to 0.4 ± 0.2% <54 mg/dL at 12 months).

Estimated HbA1c (eHbA1c), calculated from the mean glucose of rCGM, also decreased throughout the study, from 8.1 ± 0.1 at baseline to 7.5 ± 0.1% at 12 months ($p < 0.001$) (Table 2). All study points presented a statistical difference between HbA1c and eHbA1c ($p < 0.001$).

At the baseline visit, information derived from rCGM analysis generated therapeutic changes in 99% of participants. At the 12 months visit, rCGM was still informing changes in 84% of participants. These changes were categorized as either pharmacological or behavioural. Most participants (73%) had therapeutic changes simultaneously in both categories at baseline while at 12 months most (76%) had changes specific to one category. Focus on behavioural changes (as nutrition and insulin therapy education) doubled (from 10% to 20%) and focus on pharmacological changes (as type and dose of medication) more than tripled (from 17 to 56%) by 12 months.

Accordingly, the number of treatment changes was significantly higher after rCGM was introduced, increasing from 0.4 ± 0.2 in the 12-month retrospective period to 2.7 ± 0.3 changes per year at 12 months. The number of average daily SMBG did not differ from the previous 12 months period and across the intervention period (from 2.6 ± 0.1 to 2.6 ± 0.1 and 2.7 ± 0.1 strips daily).

Pharmacological changes derived from the first rCGM were focused on insulin and oral antidiabetic drugs (OAD). In line with that first evaluation, participants performed changes in dose (71%) and/or type of insulin (18%), and, to a lesser extent, changes in dose (2%) or type of OAD (6%). No other drug class was changed at the baseline visit. By the fourth rCGM, the pattern of pharmacological changes was considerably altered: Changes in insulin type were only performed by 2% of participants, while changes in insulin dose were still performed by 53%. Furthermore, information from rCGM at 12 months was related with introduction or changes in other drug classes (GLP1 analogues, DPP4 inhibitors, SGLT2 inhibitors) in 12% of participants. Participants that maintained pharmacological treatment regimen after analysis of rCGM increased from 11% at baseline to 32% at 12 months (Table 3).

After the first rCGM, 51% of participants were referred for consultation with a nurse educator which was generally for education about insulin administration. At 12 months, only 10% of participants needed to discuss specific aspects of insulin therapy and none was referred to a nursing/education consultation. Likewise, the first rCGM resulted in 50% of participants being referred for a nutrition consultation and another 7% discussed specific food counselling during rCGM review. By 12 months, none were referred to a nutrition consultation and 29% discussed aspects of their dietary plan during rCGM review (Table 3).

Table 3 Education and pharmacological therapeutic changes between the first and last visit.

	After first rCGM	After fourth rCGM
Nutrition education		
Needs addressed in consultation (%)	6.6	28.9
Referral to nutrition consultation (%)	50.0	0.0
Insulin therapy education		
Needs addressed in consultation (%)	2.2	9.9
Referral to nursing consultation (%)	51.1	0.0
Pharmacological therapy		
Change/add OAD (%)	5.6	5.6
Change OAD dose (%)	2.2	2.2
Change/add insulin type (%)	17.8	2.8
Change insulin dose (%)	70.0	53.3
Change/add GLP1 (%)	0.0	1.1
Change GLP1 dose (%)	0.0	2.2
Add iSGLT2 (%)	0.0	7.8
No drug change (%)	11.1	32.2

OAD: Oral antidiabetic agents.

Six participants reported iPro2-related adverse events (itching caused by adhesive (n = 2), increased sensitivity (n = 1), and stinging, discomfort, or mild pain at insertion site (n = 3)), nearly all of which were reported at the 12 months visit.

Self-assessed overall satisfaction with diabetes treatment increased slightly (from 27.4 ± 0.6 at baseline to 28.7 ± 0.5 at 12 months, $p < 0.05$), with 9 participants scoring low satisfaction at 12 months, while mental health, as evaluated by the GHQ-12, did not change significantly throughout the study. On the other hand, the perceived frequency of hyperglycaemia decreased significantly, with the score decreasing from 4.3 ± 0.1 at baseline to 3.3 ± 0.1 at the 12-month visit, $p < 0.05$. The perceived frequency of hypoglycaemia did not show a statistically significant difference (1.2 ± 0.1 at baseline vs. 1.5 ± 0.1 at 12 months).

Valid feedback questionnaires were obtained from 86 participants and from all healthcare professionals (9 physicians, 7 nurses, and 1 nutritionist).

Participants declared to be highly satisfied with study participation and protocol (satisfaction with sessions for placement/removal of rCGM: 5.8 ± 0.5; satisfaction with participation in the study: 5.6 ± 0.6; satisfaction with study duration: 5.4 ± 0.7; satisfaction with number of study visits: 5.4 ± 0.7), considered the use of the rCGM device globally painless and comfortable (placement/removal of rCGM device: 5.8 ± 0.5; wearing rCGM for 7 days: 5.3 ± 0.8), and felt that rCGM had a positive impact on diabetes self-management (contribution of rCGM to improve adherence to treatment: 5.4 ± 0.8; contribution of sharing and discussing rCGM data to the relation with

Table 4 Most frequent responses from persons with type 2 diabetes and healthcare professionals to the open qualitative question in the final questionnaire.

Positive	Negative
Persons with type 2 diabetes	
"It helped me understand my disease, and my behaviors. "It got me to do physical exercise!" "It taught me to do a healthier diet because I could see how the values had gone up when I ate." "It gave me motivation to control my diabetes." "It seems that I began to trust more the healthcare team. And became more at ease around them!"	"I found the device not painful, but uncomfortable." "Carrying the sensor around made me afraid." "It seemed too much time, from "reality" to "report"."
Healthcare professionals	
"Contributed to better therapeutic relationship and positive results on metabolic control." "Beneficial mainly for therapeutic adjustments in diagnoses, severe decompensations and/or abrupt changes in lifestyle." "It has contributed to better adherence to therapy […] since patients feel more involved in healthcare." "The patients themselves understood how they had to improve and why they improved." "Very important exam to be done on selected persons, with a frequency of about 2x year."	"It would be important to have more training in this area."

healthcare professionals: 5.6 ± 0.8; contribution of rCGM to understanding diabetes and related aspects: 5.5 ± 0.7; and contribution of rCGM to better manage diabetes: 5.4 ± 0.7).

From healthcare professionals, responses were positive for all four questions regarding impact of rCGM in clinical practice, namely: rCGM contributed in the process of therapeutic decision: 5.5 ± 0.2; sharing and discussing rCGM data improved relationship with participant: 5.2 ± 0.2; rCGM introduction contributed to adherence to treatment by persons with type 2 diabetes: 5.4 ± 0.2; and would other persons with type 2 diabetes benefit from rCGM use: 5.5 ± 0.2.

Most frequent responses from persons with type 2 diabetes and healthcare professionals to the open qualitative question are shown in Table 4.

Discussion

The present study shows that introducing blinded retrospective continuous glucose monitoring (rCGM) to inform clinical decision and shared goal-setting contributes to improve and sustain glycaemic control in people with insulin-treated type 2 diabetes. There was a decrease of exposure to hyperglycaemia and a decrease in glycaemic variability without a rise in hypoglycaemia. Furthermore, rCGM use fostered satisfaction and meaningful communication with the healthcare team.

In the 12 months previous to study initiation, participants evidenced deteriorating glycaemic control with few therapeutic changes, despite attending a specialized clinic staffed by a multidisciplinary team who provides considerable support regarding education and empowerment. With rCGM data available, therapeutic changes were made more frequently and targeted to changes in medication dose, timing, and/or type as well as to lifestyle resulting in a 1.3% decrease in HbA1c.

The rCGM data, along with the diary recordings made by participants during the 7 days rCGM period, provided relevant information about daily lifestyle habits and personalized metabolic responses which are frequently missing in consultation. Since concrete therapeutic choices were made together with the care team, rCGM appears to have facilitated collaborative decision-making and goal-setting [16].

The participants included in the study are a good reflection of "real world" people with type 2 diabetes under insulin therapy based on their overall demographics as well as gender-balance, socioeconomic heterogeneity, and a diverse regimen of injectable and oral medication. While age at study inclusion was limited to ≤65 years, to avoid additional barriers to technology uptake, we can expect rCGM to be similarly relevant and effective in older people [17].

These results are in line with most previous studies on the impact of continuous glucose monitoring in persons with type 2 diabetes. Those have used various devices, methodologies, and support activities, with predominant attention to real-time feedback of glucose control directly to participants [13,18–20]. In the present study, we opted for blinded rCGM, as a way to focus on patient-healthcare team communication, and to limit the interference of varying digital literacy skills [21].

Furthermore, two questions arise often in these previous studies in type 2 diabetes: identification of candidates for CGM, and optimal frequency of use [18]. By choosing to enrol participants on insulin therapy, with discrepancies between HbA1c and SMBG records, and/or complex needs, through their usual care team, we practiced a kind of pre-

screening to optimize the selection of candidates to potential benefit. As for frequency of use, all participants underwent the same rCGM usage schedule, so we cannot determine if the quadrimestral schedule is the ideal frequency. However, in comparison, Vigersky et al. showed that real-time CGM had a positive impact on glycaemic control when participants' commitment use was greater than 48 days [20]. Here, we showed a similar effect with the intermittent use of 7 days blinded CGM, to a total of 28 days across the same period. Furthermore, at the end of the intervention period, our study demonstrated a further decrease in HbA1c whereas in the Vigersky et al. study there was an attenuated effect after 24 and 52 weeks. Perhaps more importantly than optimal usage frequency, these results argues for the periodic use and interpretation of rCGM by healthcare professionals. We propose that a frequency between two and four times a year may produce optimal effects, at least in initial stages of rCGM use.

Diabetes distress is known to interfere with the implementation of digital health solutions [22], including rCGM [19]. In the present study, the assessment of treatment satisfaction and the qualitative analysis at the end of the intervention demonstrates the positive reaction of participants towards themes recognized as potential inducers of distress [16,22].

Participant commitment was further suggested by the difference in all time points between laboratorial HbA1c and rCGM-calculated HbA1c (eHbA1c). Lower eHbA1c is consistent with a greater attention by participants to adequate lifestyle and self-care habits during the 7 days of rCGM use, strengthening the role of rCGM as an educational and motivational tool. In this regard, two studies in the US suggest that the use of CGM as a "refresher", for sporadic use as an educational tool, may be not only adequate but also cost-effective [23,24].

Even with the introduction of new drug classes, insulin therapy is becoming increasingly frequent in people with type 2 diabetes. However, besides the psychological burden of being perceived as an "end of the line" drug and a personal failure, insulin therapy adjustments pose great challenges to healthcare professionals [25]. Here, the rate of therapy adjustments was at least six times more frequent in the intervention period than in the retrospective observational period, suggesting greater opportunity and confidence for treatment personalization. Furthermore, we can expect the identification of inadequate insulin injection technique, and the referral to nursing consultations for education review, to have considerable impact on insulin therapy effectiveness [25]. As structured education, and referrals to nutrition and nursing consultations, are frequently accessible during the regular follow-up at the study site, this highlights the added value provided by the rCGM.

Looking forward, standardized metrics for interpretation of CGM profiles have been recently established, as well as clinical targets proposed [26]. Furthermore, the development of the ambulatory glucose profile (AGP) currently provides a consolidated basis for the analysis and interpretation of CGM data in clinical practice [27]. Research into composite measures and digital tools to support CGM data interpretation, and even the automated pattern recognition and generation of personalized counselling for behavioural change, is expected to soon help bridge this gap [28].

The ADJUST study presents several strengths, which includes a large number of "typical" persons with type 2 diabetes on insulin therapy and the availability of retrospective data on HbA1c and therapy changes, from a period of standard care. The periodic discussion with the healthcare team assessing rCGM and the glycaemic profile, together with SMBG, introduced an educational strategy to demonstrate variability and patterns hiding behind and between infrequent SMBG measurements. This seems to have engendered, in an already highly specialized referral centre, improvements in glycaemic control along with high levels of satisfaction, and trust. Indeed, beyond HbA1c, the integration of technology and a collaborative approach are described as potentially providing gains in many aspects of patient outcomes and satisfaction [29].

On the other hand, the study presents several limitations. Mainly, the study is not an RCT. However, the historical control of a cohort attending a diabetes specialty centre over an equivalent period of time as the study period provides a reasonable and realistic "usual" care comparator. Furthermore, participants were more intensively assessed during the follow-up period, with an average of three HbA1c measurements reported the 12 months prior to the baseline evaluation, vs. four measurements available during the prospective study period (one per study visit), and the actions generated by the analysis of the rCGM generally produced a more intense support, at least in the first study visits. However, the fact that all patients were previously followed by the same healthcare team seems to support the added-value of the rCGM data on the establishment of the personalized treatment plan. Another limitation is that hypoglycaemic episodes at baseline were lower than described previously for type 2 diabetes participants on insulin therapy [30].

In summary, in persons with type 2 diabetes under insulin therapy, with inadequate glycaemic control, a structured intervention based on rCGM data interpretation produced a significant and sustained decrease in HbA1c and glucose variability through more frequent and targeted therapeutic changes. Furthermore, this was obtained without inducing an increase in hypoglycaemia episodes. Both participants and healthcare professionals identified benefits from rCGM use in terms of better shared decision-making and goal-setting, adherence to treatment, awareness and motivation, patient-healthcare team relationship, and understanding of diabetes and related factors.

Author disclosure statement

Rogério Ribeiro indicates to have no relevant conflicts of interest to disclose.

Rita Andrade indicates to have no relevant conflicts of interest to disclose.

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Declaration of competing interest

The authors declare no conflict of interest.

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