diabetesresearchandclinicalpractice 203 (2023) 110836

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Evaluation of a digital tool supporting therapeutic decision making for the personalized management of patients with type 2 diabetes not treated with insulin: A pilot study

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ARTICLE INFO

Keywords:
Personalized treatment tool
SMBG
Type 2 diabetes
Diabetes therapy

ABSTRACT

Aims: To investigate the benefits of using the Personalized Treatment Tool (PTT), a web-based clinical decision support tool assisting the diabetologist in the evaluation of patient's clinical characteristics and SMBG data, in the management of patients with non-insulin treated type 2 diabetes and inadequate glucose control.
Methods: We conducted a single-center, 16-week, cluster-randomized controlled trial.
Results: Eighty-two patients with 64.3 ± 9.4 years of age, disease duration 13.2 ± 9.1 years and HbA1c 7.8 ± 0.6%, 41 in the PTT group and 41 in the control group, completed the study. At follow-up, changes in indicators of glucose control and variability were not statistically different between the two groups. However, when considering the subgroup of patients on a single anti-diabetes drug at baseline (9 in the PTT group, 14 in the control group), changes in HbA1c and CGM-derived TIR 70–140 mg/dl, 24-hour MSG, GRADE, and HBGI were significantly improved in the PTT group compared to the control group.
Conclusion: When performed in a structured manner and used to modify the diabetes therapy through an algorithm-driven digital tool, SMBG can lead to significant improvements of glycemic control and variability in patients with type 2 diabetes not treated with insulin.

1. Introduction

Patient-centered management in health care is defined as care provision that is responsive to individual patient preferences, needs and values [1–2]. Although this approach was initially developed for use in primary care and family medicine, it is now paving its way into all branches of medicine and surgery, including diabetes care. Indeed, the American Diabetes Association and the European Association for the Study of Diabetes advocate a patient-centered approach that include the assessment of patient key characteristics and consideration of treatment-related factors possibly influencing the therapeutic decision-making process (i.e., individualized glycemic targets, effect on body weight and hypoglycemia, side effects profile of medications, complexity of the therapeutic regimen, access, cost and availability of medications) [3]. In the evaluation of patient's clinical phenotype, healthcare providers should take into account all the following aspects: a) parameters that define glycometabolic control; b) parameters related to the general clinical characteristics of the patient (duration of diabetes, age, frailty, risk deriving from hypoglycaemic episodes, overweight/obese phenotype, presence of metabolic syndrome); c) presence of specific comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, etc.); d) presence of beta-cell autoimmunity (diabetes autoimmune disease or LADA), or monogenic diabetes [3–4].

Among the parameters that define glycometabolic control, the identification of the prevalent alteration of daily glucose profiles (glycemic phenotype) as measured with self-monitoring of blood glucose (SMBG) can help the clinician choose the most appropriate glucose-lowering drug therapy [5–6]. Indeed, there are patients with prevailing fasting hyperglycemia and others with prevailing postprandial hyperglycemia [7–9]. It is also known that the individual classes of drugs

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https://doi.org/10.1016/j.diabres.2023.110836
Received 16 May 2023; Received in revised form 25 June 2023; Accepted 17 July 2023
Available online 20 July 2023

for the treatment of type 2 diabetes can be distinguished on the basis of their predominant effect on fasting (e.g., sulfonylureas, metformin, glitazones, long-acting GLP-1 RAs, long-acting insulin analogs) [10–14] or postprandial (e.g., glinides, alpha-glucosidase enzyme inhibitors, DPP-4 inhibitors, short-acting GLP-1 RAs, rapid-acting insulin analogs) [15–20] blood glucose levels.

In non-insulin-treated patients with type 2 diabetes, use of SMBG has been significantly associated with improvements in glucose control, with the reduction in HbA1c levels being greater when SMBG is performed in a structured manner and when structured SMBG data are used to adjust diabetes therapy through predefined medication algorithms [21–25]. Conducted in years 2008–2011, the Prospective Randomized Trial on Intensive SMBG Management Added Value in Non-insulin-Treated Type 2 Diabetes Mellitus Patients (PRISMA) trial randomized approximately 1,000 patients with type 2 diabetes treated with oral agents and/or diet to either intensive structured monitoring (ISM) or discretionary SMBG showing that the reduction in HbA1c is larger with the former [23]. Notably, in the ISM group the SMBG data were downloaded from the glucometer and analyzed through ad hoc software providing easy-to-read summary statistics and non-binding suggestion for changes in diabetes medication based on the predefined algorithm of the trial [26].

Given the availability of new classes of medications with clear evidence of benefit upon glycemic and extraglycemic outcomes, we have developed a novel clinical decision support tool, the so-called Personalized Treatment Tool (PTT), which assists the diabetologist in the evaluation of clinical characteristics and SMBG data of patients with type 2 diabetes, and guides in the choice of the most appropriate anti-diabetes drug therapy for each individual patient.

To evaluate the benefits of using PTT in the outpatient setting, we conducted a single-centre, 16-week, cluster-randomized controlled trial recruiting patients with non-insulin treated type 2 diabetes and inadequate glycometabolic control.

2. Methods

2.1. Study design

Starting on September 2019, all patients being referred to the Endocrinology Unit of the University Hospital "Consorziale Policlinico" of Bari, Italy, were consecutively evaluated for eligibility within an already-scheduled visit at the diabetes center.

Inclusion criteria were type 2 diabetes, >40 years of age, treatment with oral or non-insulin based injectable drugs in addition to lifestyle intervention, HbA1c 7.0–10.5%, willingness to perform structured SMBG with the prescribed periodicity and to wear a continuous glucose monitoring (CGM) device for a total of two weeks across the study period.

On January 12, 2021, a minor amendment to study protocol was submitted to the Institutional Ethics Committee. As a result, patients were enrolled with HbA1c values between 7.5% and 10.5% to achieve a slightly higher baseline HbA1c value of the enrolled population.

Exclusion criteria were: any type of insulin-based therapy, diagnosis of psychiatric diseases that could compromise adherence to the study protocol, severe chronic renal failure (eGFR < 30 mL/min/1.73 m^2), severely impaired hepatic function, severe respiratory insufficiency, clinically relevant morbidity of the cardiovascular, gastrointestinal, genitourinary or nervous system arisen in the 6 months preceding the study start, uncontrolled arterial hypertension (PAS > 180 mmHg, PAD > 100 mmHg), presence of active neoplasm or history of chemo- and radiotherapy within 5 years prior to the study start, pregnancy or breastfeeding, any other medical or psychological condition which in the opinion of the investigators could make the patient unable to comply fully with the trial procedures.

After giving informed consent, eligible patients were allocated either in the intervention arm (PTT, personalized treatment tool) or the control arm (UC, usual care) based on the name of the physician (cluster) they had been randomly assigned to at the visit check-in. The physicians of the diabetes center, in turn, were randomly divided into two groups, the first evaluating the patients through the PTT, the other following the usual clinical practice, i.e., evaluation of diabetes laboratory tests, patient's clinical characteristic, and SMBG paper diaries without any computer-based elaboration nor predefined algorithm for diabetes therapy changes.

The study protocol was submitted to the Institutional Ethics Committee of the University Hospital "Consorziale Policlinico" of Bari (protocol no. 20875, approved on February 6, 2019) and carried out in adherence to Good Clinical Practice, ICH Harmonized Tripartite Guidelines for Good Clinical Practice and Declaration of Helsinki.

2.2. Personalized treatment tool

The PTT is a web application that is accessible on the Internet with login.

When initiating a new patient evaluation, the health care professional is asked to enter some personal and clinical information of the patient (age, sex, ethnic origin, duration of disease, weight, height, last HbA1c value, last creatinine value, history of atherosclerotic cardiovascular events or heart failure, previous diagnosis of diabetic nephropathy/chronic kidney disease, diabetes medications in use). The application in turn elaborates and presents this information in dedicated panels of a dashboard with a traffic light color-code to highlight those aspects that deserve particular attention. The PTT can also acquire the SMBG data directly from the patient's glucometer, evaluate if the number of readings is adequate (based on a predefined number/week), classify the readings as pre- or postprandial, and calculate easy-to-understand indicators of glycemic control and variability such as 24-hour average blood glucose (BG), median fasting BG, median postprandial BG, median glycemic excursion at meals, and the total number of hypoglycemic events during the reference time period. The PTT distinguishes anti-diabetes drugs based on their relative efficacy on fasting versus postprandial hyperglycemia (expressed by a numerical index, the so-called Hyperglycemia Efficacy Index [HEI], which was calculated based on data available in the scientific literature; Table S1), the efficacy in reducing glycemic excursions at meals, and the probability with which they can induce hypoglycemia (defined with an ad hoc risk score, the so-called Hypoglycemia Risk Index [HRI]; Table S1). When the frequency of SMBG is appropriate, the PTT is able to identify the patient's prevailing glycemic alteration and express it with a numerical index that takes into account the extent by which median fasting and 2-hour postprandial BG readings, respectively, exceed their target values (100 mg/dL for fasting glucose and 140 mg/dL for postprandial glucose, not modifiable), and count the number of SMBG-documented hypoglycemic events that occurred in the predefined period. When median fasting BG, median postprandial BG, median glycemic excursion at meals or number of hypoglycemic events exceed the predefined thresholds for modification of drug therapy, the application generates a list of drug classes (ranked from most effective to least effective, based on the comparison of the indices that define the action of the drug and those that describe patient prevailing glycemic alteration, or from safer to less safe) that should be added or replaced in the previous therapeutic regimen to improve glycemic control and/or avoid recurrent hypoglycemia. The application does not show as available options drugs already in use, combinations that are not allowed, and contraindicated drugs in case of low eGFR values, and highlights those classes of drugs with documented benefits on cardiovascular outcomes and/or renal outcomes and/or body weight loss. The user/health care professional can therefore select the most appropriate therapy and the dosages of each individual drug based on the rank of drugs proposed by the application and patient clinical characteristics as highlighted in the dashboard (Figure S1).

2.3. Procedures

After acquiring informed consent from participants, the investigators collected the following information: near and distant medical history, drugs in use for the treatment of diabetes, anthropometric parameters, recent creatinine and HbA1c values (measured in the previous two weeks). Patients were given a glucometer with its compatible strips (Accu-Chek Guide, Roche Diabetes Care, Indianapolis, IN, USA) and were asked to perform a six-point SMBG profile (before and 2 h after the meal) once a week for consecutive 16 weeks.

At Week 4 patients were asked to wear a professional CGM device (Dexcom G4 PLATINUM, Dexcom Inc., San Diego, CA, USA) for 7 days and take at least two BG readings per day for CGM calibration. At Day 29 SMBG data were downloaded with Accu-Chek Smart Pix device reader and software, and CGM data with the Dexcom STUDIO software. Patients were evaluated for possible modification of diabetes drug therapy according to allocation group, i.e. with the support of the PTT or following the normal clinical practice. Notably, only SMBG and not CGM data were available for evaluation at this time point. At Week 10 patients underwent a second 7-day CGM period, and at Day 71 both SMBG and CGM data were collected for comparison with those obtained at Day 29. A new HbA1c measurement was scheduled to be done at the same laboratory as baseline at Week 16. The timeline of the study is illustrated in Figure S2.

2.4. Study endpoints

A relevant study endpoint was change in time in glucose range (TIR) 70–140 mg/dL, evaluated from the CGM data at Week 10 of the study as compared to Week 4. Other efficacy endpoints of the study were changes in TIR 70–180 mg/dL, time > 180 mg/dL, time < 70 mg/dl, 24-hour mean sensor glucose (MSG), and indices of glycemic variability including the Coefficient of Variation of mean glucose (CV), Mean Amplitude of Glycemic Excursions (MAGE), Average Daily Risk Ratio (ADRR), J-Index, M-value, Low Blood Glucose Index (LBGI), High Blood Glucose Index (HBGI), Continuous Overlapping Net Glycemic Action (CONGA), Mean of Daily Differences (MODD), Glycemic Risk Assessment in Diabetes Equation (GRADE), and Mean Absolute Glucose (MAG), all evaluated from CGM data at Week 10 of the study as compared to Week 4, and change in HbA1c, evaluated at end of study as compared to baseline.

2.5. Statistical methods

The projected sample size was computed using the time spent in the 70–140 mg/dL glucose range as the benchmark variable, although the nature of a pilot study makes the definition of a primary endpoint non-essential. In the specific case, the choice of a total of 76 patients completing the study (38 per group) guarantees a power equal to 0.80 assuming a mean difference between the two study groups equal to 1139 min − 958 min = 181 min with standard deviations equal to 231 for the intervention group and 315 for the control group. The estimates used (mean and SD) were extrapolated from the study by Guerci et al. [27]. The calculations were performed assuming a level of significance equal to 0.05 and using a two-tailed independent sample *t*-test. In the end assuming a drop-out rate of 10%, the sample size total was increased to 86 patients.

In general, continuous variables were expressed as mean ± standard deviation, median, minimum and maximum values, while discrete variables as absolute and percentage frequencies. General Linear Models (GLM) with change from baseline to follow-up as dependent variable and Group (PTT, Control) as independent variable were employed to test the differences between the two Groups in changes in indicators of glycemic control and variability. For all the other analyses, unless otherwise indicated, Student *t*-test (for independent or paired samples, as appropriate) and the Chi-square test were used to evaluate differences in continuous and discrete variables, respectively. All statistical analyses were carried out using SAS software version 9.4. Two-tailed P-values < 0.05 were considered statistically significant.

3. Results

From September 2019 to June 2021, 108 patients were enrolled, of which 25 voluntarily withdrew from the study (4 due to the spread of Sars-Cov-2 pandemic), and another patient went lost at follow up. Eighty-two patients, 41 in the PTT group and 41 in the control group, completed the study and were therefore included in the final analysis.

The main demographic and clinical characteristics of the patients who completed the study are summarized in Table 1. At the time of enrollment, patients had 64.3 ± 9.4 years of age, BMI 29.8 ± 5.9 kg/m^2, disease duration 13.2 ± 9.1 years, HbA1c 7.8 ± 0.6%. A minority of the patients had a history of atherosclerotic cardiovascular disease (12.2%), heart failure (1.2%) or diabetic nephropathy (9.8%), the latter defined

Table 1
Baseline characteristics of study participants.

Variable	Control (n = 41)	PTT (n = 41)	All Patients (n = 82)	P-value
Age, years				
Mean ± SD	63.07 ± 10.74	65.54 ± 7.68	64.3 ± 9.36	0.2357
Median (Min - Max)	64 (39–82)	65 (46–78)	65 (39–82)	
Diabetes duration, years				
Mean ± SD	13.61 ± 9.92	12.85 ± 8.39	13.23 ± 9.14	0.7103
Median (Min - Max)	12 (1–40)	11 (1–33)	11.5 (1–40)	
BMI, kg/m^2				
Mean ± SD	30.34 ± 6.67	29.19 ± 5.1	29.76 ± 5.93	0.3837
Median (Min - Max)	29.4 (18.9–47)	28.8 (20.7–38.9)	28.9 (18.9–47)	
Creatinine, mg/dl				
Mean ± SD	0.89 ± 0.21	0.88 ± 0.21	0.88 ± 0.21	0.8709
Median (Min - Max)	0.89 (0.57–1.55)	0.89 (0.46–1.25)	0.89 (0.46–1.55)	
GFR, ml/min				
Mean ± SD	88.95 ± 21.06	82.82 ± 16.49	85.89 ± 19.05	0.1462
Median (Min - Max)	90 (53–154)	84.5 (56.2–116)	86.1 (53–154)	
≥90, n (%)	21 (51.2)	18 (43.9)	39 (47.6)	0.8853
60–89, n (%)	17 (41.5)	20 (48.8)	37 (45.2)	
30–59, n (%)	3 (7.3)	3 (7.3)	6 (7.3)	
15–29, n (%)	0 (0)	0 (0)	0 (0)	
<15, n (%)	0 (0)	0 (0)	0 (0)	
HbA1c, %				
Mean ± SD	7.69 ± 0.58	7.85 ± 0.65	7.77 ± 0.62	0.2550
Median (Min - Max)	7.6 (7.09–10.4)	7.6 (7–9.7)	7.6 (7–10.4)	
Gender (Female), n (%)	13 (31.7)	13 (31.7)	26 (31.7)	1.0000
ASCVD, n (%)	5 (12.2)	5 (12.2)	10 (12.2)	1.0000
HF, n (%)	0 (0)	1 (2.4)	1 (1.2)	0.3143
DKD, n (%)	1 (2.4)	7 (17.1)	8 (9.8)	0.0255
OAD, n				
1, n (%)	14 (34.1)	9 (22)	23 (28)	0.1703
2, n (%)	20 (48.8)	28 (68.3)	48 (58.5)	
3, n (%)	7 (17.1)	3 (7.3)	10 (12.2)	
4, n (%)	0 (0)	1 (2.4)	1 (1.2)	
Biguanides, n (%)	37 (90.2)	41 (100)	78 (95.1)	0.1158
Glitazones, n (%)	8 (19.5)	5 (12.2)	13 (15.9)	0.5468
Sulphonylureas, n (%)	1 (2.4)	1 (2.4)	2 (2.4)	1.000
Glinides, n (%)	2 (4.8)	1 (2.4)	3 (3.7)	1.000
DPP-4i, n (%)	6 (14.6)	7 (17.1)	13 (15.9)	1.000
GLP-1 RA, n (%)	14 (34.1)	18 (43.9)	32 (39)	0.4974
SGLT-2i, n (%)	7 (17.1)	5 (12.2)	12 (14.6)	0.7560

ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; DKD, diabetic kidney disease; OAD, oral anti-diabetes drug; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors.

by eGFR < 60 mL/min/1.73 m^2 or early morning urine albumin/creatinine ratio > 30 mg/g. Twenty-three patients (28.0%) were treated with a single diabetes drug, while the remainder were treated with two or more drugs. There were no significant differences between the patients assigned to the two study groups except for prevalence of nephropathy.

In the PTT group, 22 patients (53.6%) underwent the addition of a new anti-diabetes drug, 4 patients (9.8%) a dose increase of the drug, 9 patients (22.0%) the replacement of a drug with another one, and 6 patients (14.6%) no change in drug therapy. In the control group, 20 patients (48.8%) underwent drug addition, 3 patients (7.3%) dose increase, 17 patients (41.5%) drug replacement, and only one patient (2.4%) no change in drug therapy. Prevalence of use of anti-diabetes medications after V2 is illustrated in Table S2.

At Week 10, statistically significant improvements in TIR 70–140 mg/dl, time > 140 mg/dl, GRADE - % Euglycemic, and GRADE - % Hyperglycemic were observed in both groups as compared with Week 4, and in the PTT group significant improvements in TIR 70–180 mg/dl and time > 180 mg/dl, 24-hour MSG, CONGA 2-hour, CONGA 4-hour, GRADE, HBGI, and J-Index were also reported (Table 2). Furthermore, a statistically significant reduction in HbA1c was observed in both groups at the end of the study as compared to the baseline (PTT: −0.95 ± 0.89%; control: −0.82 ± 0.92%). The variations of these indicators were greater in number in the PTT group, but the difference between the two groups did not reach statistical significance (Fig. 1; Table 2).

Based on the results of an interim analysis evaluating the effect of certain clinical variables (i.e., age, diabetes duration, HbA1c level and diabetes therapy at baseline) on treatment outcomes, a subgroup analysis was conducted in patients with a single anti-diabetes drug at baseline. Of note, when considering this specific subgroup of patients (9 in the PTT group, 14 in the control group), improvements of TIR 70–140 mg/dl, 24-hour MSG, GRADE, and HBGI were significantly greater in the PTT group than in the control group (Fig. 2; Table 3). The PTT group also reported the greatest reduction in HbA1c from baseline in these patients (1.60 ± 0.90% vs. 0.84 ± 0.72%, p = 0.0365).

Treatment adherence was self-reported. Of note, two patients, one per group, actually took half of the recommended dose. Moreover, one patient in the intervention group reported inability to retrieve the prescribed drug and three in the control group experienced drug intolerance shortly after V2, and an additional visit was scheduled for drug substitution. Finally, three patients, one in the intervention group and two in the control group, reported clinically relevant hyperglycemia at V4 such that further intensification of therapy was offered through the PTT and following usual care, respectively.

4. Discussion

The results of this pilot study suggest that the use of the PTT to assist clinical evaluation of patients with type 2 diabetes not treated with insulin may be potentially beneficial, resulting in clinically significant improvements in glycemic control and variability. The major strength of this experimental design was the use of professional CGM to catch short-term changes in the innovative glucose metrics, such as time spent in or out of target glucose range, 24-hour MSG and sophisticated indices of glycemic variability [28]. Evidence and expert consensus support the use of professional (blinded) CGM for studies that recruit only CGM-naive participants to assess the efficacy of an investigational drug or device [29]. Among CGM-derived metrics, TIR is easy to understand, quickly responsive to changes in lifestyle and drug therapy, and now considered to be complementary to HbA1c measurement when assessing glycemic control and variability [29–30]. Of note, TIR 70–140 mg/dl, also known as time in tight range, has recently emerged as a reported measure of TIR in people with type 2 diabetes using glucose-lowering agents [29].

The results obtained in the patients who were taking a single anti-diabetes medication at baseline are noteworthy. Indeed, this subgroup

Table 2
Between-group comparisons of CGM-derived measures of glycemic variability (changes from baseline).

Outcome	Control	PTT	P-value
CV, %			
Mean ± SD (n)	−0.58 ± 5.78 (41)	0.09 ± 5.62 (41)	0.5949
Median (Min - Max)	−0.55 (-11.03–19.98)	−0.82 (-17.1–10.95)	
CONGA 1-hour			
Mean ± SD (n)	−1.16 ± 6.53 (41)	−1.03 ± 5.88 (41)	0.9219
Median (Min - Max)	−1.41 (-13.72–14.81)	−0.47 (-19.21–13.49)	
CONGA 2-hour			
Mean ± SD (n)	−2.76 ± 9.55 (41)	−3.3 ± 9.57 (41)	0.7969
Median (Min - Max)	−3.17 (-25.69–20.59)	−3.07 (–33.22–17.88)	
CONGA 4-hour			
Mean ± SD (n)	−3.51 ± 13.51 (41)	−5.29 ± 12.26 (41)	0.5321
Median (Min - Max)	−2.22 (-39.5–32.32)	−5.4 (-40.33–17.67)	
J-Index			
Mean ± SD (n)	−1.99 ± 10.78 (41)	−6.07 ± 12.95 (41)	0.1249
Median (Min - Max)	−2.99 (–32.89–25.69)	−4.69 (-49.99–15.3)	
LBGI			
Mean ± SD (n)	0.14 ± 0.68 (41)	0.16 ± 0.87 (41)	0.8958
Median (Min - Max)	0.08 (-2.19–3.02)	0.07 (-3.14–3.38)	
HBGI			
Mean ± SD (n)	−0.36 ± 2.87 (41)	−1.68 ± 3.96 (41)	0.0898
Median (Min - Max)	−0.91 (-7.88–9.25)	−0.79 (-17.72–4.45)	
GRADE			
Mean ± SD (n)	−0.59 ± 2.83 (41)	−1.75 ± 3.34 (41)	0.0934
Median (Min - Max)	−0.94 (-8.36–6.56)	−1.18 (-13.85–4.58)	
GRADE - % Euglycemic			
Mean ± SD (n)	7.7 ± 17.22 (41)	9.91 ± 19.3 (41)	0.5848
Median (Min - Max)	6.96 (-24.33–50.15)	5.87 (-36.38–55.7)	
GRADE - % Hyperglycemic			
Mean ± SD (n)	−8.81 ± 16.53 (41)	−10.88 ± 20 (41)	0.6107
Median (Min - Max)	−7.26 (-51.66–24.42)	−8.15 (-57.26–36.94)	
GRADE - % Hypoglycemic			
Mean ± SD (n)	1.11 ± 5.16 (41)	0.96 ± 8.12 (41)	0.9232
Median (Min - Max)	0 (-6.44–21.51)	0 (-27.46–37.62)	
MODD			
Mean ± SD (n)	−0.16 ± 8.8 (39)	−1.85 ± 6.6 (40)	0.3366
Median (Min - Max)	−0.26 (-20.9–23.49)	−1.47 (-25.32–15.07)	
MAGE-up			
Mean ± SD (n)	−5.28 ± 17.72 (41)	−4.29 ± 17.03 (41)	0.7987
Median (Min - Max)	−7.65 (-45.76–27.82)	−1.96 (-70.57–24.57)	
MAGE-down			
Mean ± SD (n)	−3.8 ± 17.79 (41)	−3.72 ± 13.68 (41)	0.9819
Median (Min - Max)	−3.08 (-38.51–47.13)	−5.82 (-34.06–24.25)	
ADRR			
Mean ± SD (n)	−0.73 ± 11.56 (41)	−2.99 ± 9.65 (41)	0.3385
Median (Min - Max)	−2.74 (-16.36–50.33)	−0.51 (-40.24–15.25)	
M−Value			
Mean ± SD (n)	0.2 ± 4.53 (41)	−1.81 ± 6.31 (41)	0.1014
Median (Min - Max)	−0.17 (-8.08–17.13)	−0.47 (-27.87–5.14)	
MAG			
Mean ± SD (n)	0.77 ± 11 (41)	0.27 ± 7.81 (41)	0.8138
Median (Min - Max)	0.61 (-18.95–30.73)	1.39 (-20.56–16.9)	

CV, coefficient of variation; ADRR, average daily risk ratio; CONGA, continuous overlapping net glycemic action; GRADE, glycemic risk assessment in diabetes equation; HBGI, high blood glucose index; LBGI, low blood glucose index; MAG, mean absolute glucose; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences.

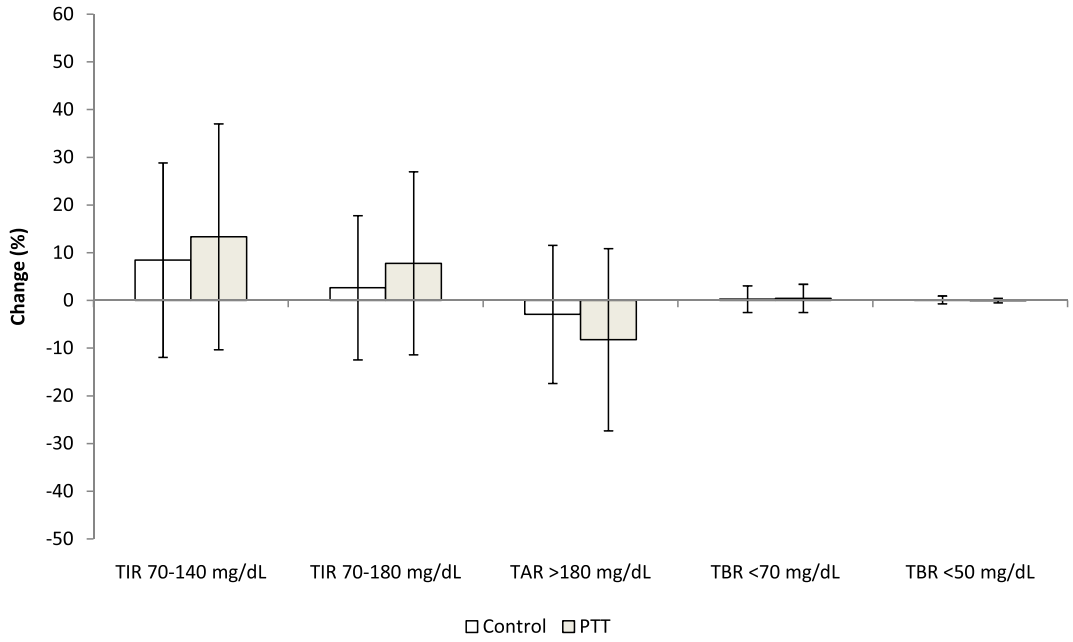

Fig. 1. Between-group comparisons of CGM-derived time spent within and outside prespecified glucose ranges (changes from baseline) in the total cohort of patients. Legend: TIR, time in range; TAR, time above range; TBR time below range; PTT, personalized treatment tool.

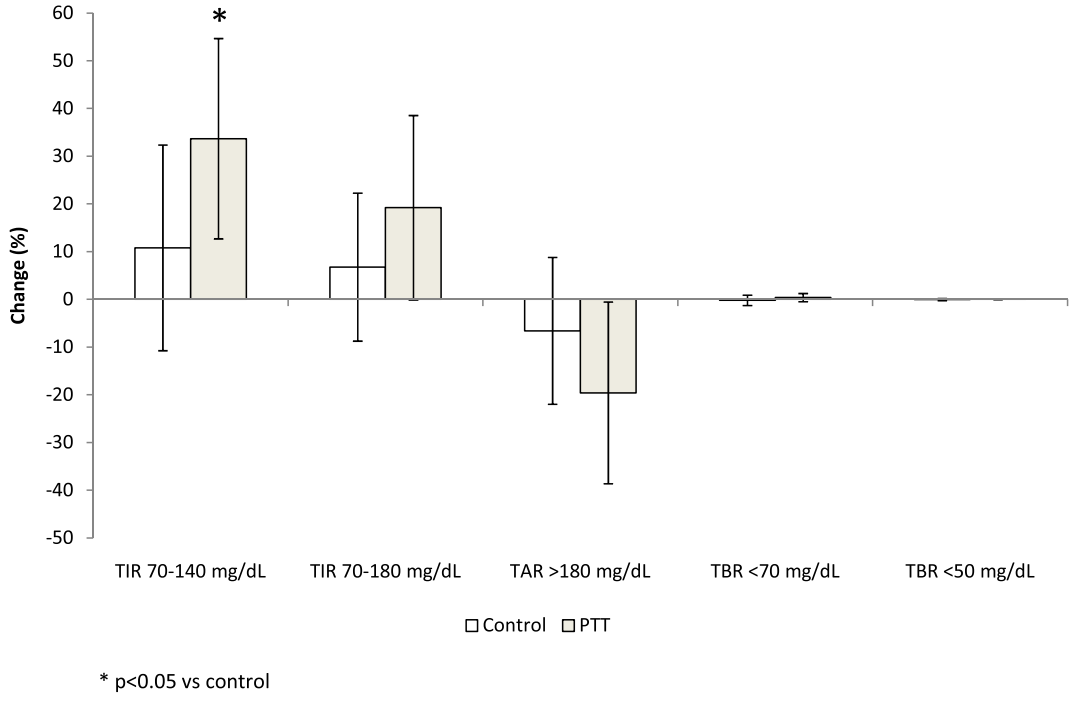

Fig. 2. Between-group comparisons of CGM-derived time spent within and outside prespecified glucose ranges (changes from baseline) in the subgroup of patients taking a single anti-diabetes medication at baseline. Legend: TIR, time in range; TAR, time above range; TBR time below range; PTT, personalized treatment tool.

may represent an ideal population to evaluate the efficacy of the PTT since the effect of other factors, not related to the clinical characteristics of the patient but still conditioning the choice of the pharmacological therapy, for example the reimbursement of innovative drugs (DDP-IV inhibitors, GLP-1 RA and SGLT-2 inhibitors) by the Italian National Healthcare System that, at the time this study was carried out, was limited to some combination therapies and not others, may be considered negligible. In these patients, the use of PTT was associated to a three-fold increase in TIR 70–140 mg/dl compared to conventional management (32.2 ± 20.1% vs 10.9 ± 21.0%, p = 0.0249). It should be noted, however, that these results refer only to 23 subjects, 9 in the PTT group (22.0%) and 14 in the control group (34.1%), and therefore need to be confirmed in larger cohorts of patients and/or studies specifically recruiting patients on monotherapy with anti-diabetes agents to validate the role of PTT in clinical practice.

This study has some limitations. Firstly, it was conducted at a center of reference for the treatment of diabetes, therefore all the physicians involved in the trial, including those who acted without the support of the PTT, shared a very good knowledge of the different classes of drugs and attention to a person-centered approach to care. We can therefore

Table 3
Between-group comparisons of CGM-derived measures of glycemic variability (changes from baseline) in the subgroup of patients taking a single anti-diabetes medication at baseline.

Variable	Control	PTT	P-value
CV, %			
Mean ± SD (n)	−1.83 ± 5.5 (14)	−2.2 ± 1.29 (9)	0.8459
Median (Min - Max)	−1.98 (-9.81–9.56)	−2.17 (-4.07 - −0.47)	
ADRR			
Mean ± SD (n)	−1.96 ± 11 (14)	−8.29 ± 4.67 (9)	0.1195
Median (Min - Max)	−2.49 (-16.23–23.66)	−8.65 (-16.27–0.13)	
CONGA 1-hour			
Mean ± SD (n)	−1.26 ± 8.65 (14)	−4.62 ± 4.89 (9)	0.3028
Median (Min - Max)	−1.62 (-13.72–14.81)	−5.89 (-14.81–0.57)	
CONGA 2-hour			
Mean ± SD (n)	−4.09 ± 12.01 (14)	−9.1 ± 7.51 (9)	0.2776
Median (Min - Max)	−5.32 (-25.69–20.59)	−10.12 (–22.26–1.53)	
CONGA 4-hour			
Mean ± SD (n)	−6.95 ± 15.76 (14)	−13.93 ± 9.56 (9)	0.2469
Median (Min - Max)	−7.38 (-39.5–24.44)	−13.74 (-29.42 - −0.07)	
GRADE - % Euglycemic			
Mean ± SD (n)	11.82 ± 18.65 (14)	26.74 ± 17.7 (9)	0.0701
Median (Min - Max)	13.2 (-19.89–50.15)	17.54 (5.87–55.7)	
GRADE - % Hyperglycemic			
Mean ± SD (n)	−11.39 ± 18.86 (14)	−27.26 ± 17.59 (9)	0.0564
Median (Min - Max)	−9.43 (-51.66–19.89)	−17.79 (-57.26 - −8.81)	
GRADE - % Hypoglycemic			
Mean ± SD (n)	−0.43 ± 2.26 (14)	0.52 ± 1.05 (9)	0.2539
Median (Min - Max)	0 (-6.44–1.55)	0 (-0.19–2.94)	
GRADE			
Mean ± SD (n)	−1.4 ± 2.98 (14)	−4.15 ± 2.93 (9)	0.0412
Median (Min - Max)	−1.44 (-8.36–3.14)	−3.41 (-9.6 - −1.18)	
HBGI			
Mean ± SD (n)	−1.11 ± 3.03 (14)	−4.29 ± 4.04 (9)	0.0428
Median (Min - Max)	−0.99 (-7.88–3.69)	−3.14 (-11.25 - −0.78)	
LBGI			
Mean ± SD (n)	0.12 ± 0.4 (14)	0.21 ± 0.28 (9)	0.5569
Median (Min - Max)	0.11 (-0.69–0.92)	0.09 (-0.01–0.78)	
J-Index			
Mean ± SD (n)	−5.15 ± 12.28 (14)	−16.07 ± 13.3 (9)	0.0568
Median (Min - Max)	−5.28 (–32.89–14.8)	−11.61 (-40.43 - −5.19)	
M−Value			
Mean ± SD (n)	−1.02 ± 3.72 (14)	−5.34 ± 7.46 (9)	0.0778
Median (Min - Max)	−0.26 (-8.08–6.09)	−2.72 (-21.21–0.34)	
MAG			
Mean ± SD (n)	3.12 ± 15 (14)	−2.54 ± 7.75 (9)	0.3103
Median (Min - Max)	0.86 (-18.95–30.73)	−0.1 (-20.14–4.4)	
MAGE-up			
Mean ± SD (n)	−8.55 ± 20.7 (14)	−16.79 ± 6.27 (9)	0.2618
Median (Min - Max)	−8.2 (-45.76–27.82)	−15.62 (-31.77 - −12.09)	
MAGE-down			
Mean ± SD (n)	−8.16 ± 23.1 (14)	−15.65 ± 6.53 (9)	0.3570
Median (Min - Max)	−8.76 (-38.51–41.32)	−15.33 (-24.16 - −2.51)	
MODD			
Mean ± SD (n)	0.02 ± 12.26 (14)	−5.14 ± 3.48 (9)	0.2358
Median (Min - Max)	−2.19 (-20.9–23.49)	−4.43 (-10.16–0.11)	

CV, coefficient of variation; ADRR, average daily risk ratio; CONGA, continuous overlapping net glycemic action; GRADE, glycemic risk assessment in diabetes equation; HBGI, high blood glucose index; LBGI, low blood glucose index; MAG, mean absolute glucose; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences.

assume that the difference between the two groups could have been greater if the study had been conducted in a center with less expertise or even in a non-specialist setting, such as in primary care. Secondly, enrolled patients were in discrete glycometabolic control prior to study start (baseline HbA1c 7.77%). Different therapeutic choices and glycemic outcomes would have probably been observed if patients had presented higher levels of hyperglycemia at baseline. As an example, in the PTT group, 6 patients did not show sufficient alterations in the glycemic profile to exceed the established thresholds for the algorithm to suggest and thus perform a modification of drug therapy, while, in the control group, only in one case the investigator chose to confirm the drugs in use, considering the patient's glucose profiles to be satisfactory. To limit such imbalances between the two groups, starting on January 2021, the minimum level of HbA1c for recruitment was raised from 7.0% to 7.5%. Thirdly, although formally sized with 80% power, it is important to keep in mind that this is a pilot study aimed to generate hypotheses rather than to confirm them. Fourthly, to be included in the study, the patients needed to be able to use properly the professional CGM device, and in particular to handle the receiver for entering the glucose values required for the device's daily calibration, and this has certainly constituted a bias in patient selection. Finally, as patients with severe diabetes-related complications and/or comorbidities were excluded from the trial, and prevalence of ASCVD, HF and DKD in the study population was generally low, efficacy and safety of the PTT in cohorts of patients with higher burden of morbidity are still to be determined.

International guidelines for the treatment of hyperglycemia in patients with type 2 diabetes recommend the introduction of drugs with proven cardiovascular and/or renal benefits in patients with certain comorbidities (disease cardiovascular arteriosclerosis, heart failure, chronic kidney disease) or indicators of high cardiovascular risk, regardless of the value of the HbA1c [31–33]. The guidelines of American Diabetes Association also recommend the use of GLP-1 RAs that are more effective on weight reduction and/or SGLT-2 inhibitors when HbA1c is above the individualized target and there is a need to limit further weight gain or promote weight loss, and to consider the introduction of sulfonylureas and/or insulin only as the last option when it is a priority to minimize the risk of hypoglycemia [32]. We believe that the evaluation of structured SMBG data can help the diabetologist choose the most appropriate therapy when improving glycemic control is one of the goals to be pursued in patients with prevalent fasting or postprandial hyperglycemia, and to avoid hypoglycemia in patients treated with sulfonylureas and/or glinides. The PTT, through highlighting the salient clinical characteristics of the patient and proposing a list of possible therapeutic alternatives based on the prevailing alteration(s) of the daily glycemic profiles, on the action profile of the different classes of drugs and on the risk of hypoglycemia associated with them, can therefore favor the personalized management of type 2 diabetes and overcome therapeutic inertia, particularly in the primary care setting.

In recent years, the advent of personal CGM systems showing, automatically and several times a day, the current glucose value, the graph of the latest readings and the future trend, has revolutionized the management of diabetes, with increasingly robust evidence suggesting their beneficial effects also in patients with type 2 diabetes who are on non-intensive insulin therapy regimens or treated with non-insulin-based drugs [34–35]. Nonetheless, SMBG remains the method most frequently prescribed by clinicians, as well as that most commonly reimbursed by national healthcare systems, for monitoring glucose levels in this type of patients.

5. Conclusion

Appropriate assessment of structured SMBG data and patient's clinical characteristics through a digital tool can result in more effective

changes in diabetes drug therapy and provide significant improvement of glycemic control and variability in patients with type 2 diabetes not treated with insulin, at least in those on monotherapy with anti-diabetes agents.

Author contributions

FG designed and supervised the study. SDM created the dataset. EB conducted statistical analysis. SDM prepared the first draft of the manuscript. All authors read, provided feedback, and approved the final manuscript. FG is the guarantor and takes responsibility for the contents of the article.

Funding

This study was funded unconditionally by Roche Diabetes Care Italy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We gratefully acknowledge Dr. Nicola Morea, Anna Montedoro, Mariangela Caporusso, Giovanni Dambrosio, Francesca Guarini, Giulia Le Grazie, Alessandro de Bari (Section of Internal Medicine, Endocrinology, Andrology, and Metabolic Diseases, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari Aldo Moro, Bari, Italy) for their contribution in the conduct of the study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110836.

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