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ORIGINAL ARTICLE

Impact of the "Diabetes Interactive Diary" Telemedicine System on Metabolic Control, Risk of Hypoglycemia, and Quality of Life: A Randomized Clinical Trial in Type 1 Diabetes

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Abstract

Background: Telemedicine systems based on mobile phones represent new promising educational tools. The "Diabetes Interactive Diary" (DID) is a carbohydrate/bolus calculator promoting the patient–physician communication via short message service. This study aimed to compare the efficacy of the DID versus usual care on metabolic control, hypoglycemia, and quality of life.

Patients and Methods: Patients with type 1 diabetes on a basal:bolus regimen with insulin glargine and insulin glulisine, not previously educated on carbohydrate (CHO) counting, were randomized to DID (Group A; $n=63$) or traditional education (Group B; $n=64$). Generalized hierarchical linear regression models for repeated measures were applied to compare changes between groups. Incidence of hypoglycemia was compared using Poisson regression models.

Results: Of 127 patients (age, 36.9 ± 10.5 years; diabetes duration, 16.3 ± 9.3 years), 15 (11.8%) dropped out. After 6 months, hemoglobin A1c (HbA1c) levels decreased by -0.49 ± 0.11 in Group A and -0.48 ± 0.11 in Group B ($P=0.73$). Group A showed a 86% lower risk of grade 2 hypoglycemia than Group B. Compared with usual care, DID improved the "perceived frequency of hyperglycemic episodes" scale of the Diabetes Treatment Satisfaction Questionnaire and the "social relations" and the "fear of hypoglycemia" dimensions of the Diabetes Specific Quality of Life Scale. Results obtained with DID markedly differ among patients and centers.

Conclusions: DID is no more effective than traditional CHO counting education in reducing HbA1c levels. DID reduces the risk of moderate/severe hypoglycemia and improves quality of life. A better understanding of patients' and healthcare professionals' attitudes associated with an effective care supported by technology is essential to avoid waste of resources.

Introduction

Besides pharmacological treatments, patient education is an integral part of the diabetes care to teach a healthy lifestyle and an appropriate nutrition for the control of blood glucose levels and body weight.[1,2] Although the role of education is widely recognized, evidence of a global insufficient access to educational support clearly emerges from the analysis of quality of care data in type 1 diabetes. Data from routine clinical practice show that one in two patients with type 1 diabetes have levels of hemoglobin A1c (HbA1c) above 8% and one in five have a body mass index above 27 kg/m^2, whereas in type 2 diabetes one in two patients have levels of HbA1c above 7%, and about 60% are overweight or obese.[3] The complexity of the information to be taught,[4] a suboptimal organization of the healthcare system and/or the allocation of

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resources devoted to educational activities,[5] and patient-related psychosocial factors could be the main reasons for these unsatisfactory outcomes. In this respect, the Diabetes Attitudes, Wishes, and Needs (DAWN) initiative in 13 countries identified a major gap between the educational support needs of people with diabetes and the care and support available in the different countries. The study documented a substantial lack of critical resources for education, in particular skill, time, and adequate referral sources.[6,7] Furthermore, different psychosocial factors (e.g., poor adherence to treatment, distress, poor self-efficacy, and lack of motivation) that negatively influence clinical outcomes can be effectively addressed through appropriate self-management education with significant improvements in terms of therapeutic goals and quality of life.[8,9]

As part of education of patients treated with insulin, carbohydrate (CHO) counting represents a main strategy.[4–11] It is immediately translated into a flexible insulin therapy and insulin dose adjustment, thus improving dietary freedom, quality of life, and glycemic control, without increasing the rate of severe hypoglycemia or cardiovascular risk.[12] Nevertheless, flexible diet and insulin therapy require complex training for patients, who need to be educated in the type and amount of CHO found in foods, portion estimation, glycemic index, relationships among blood glucose levels and food/diabetes medication/physical activity, CHO/insulin ratio, and specific algorithms to adjust insulin doses.[10,13] The complexity of this educational approach limits a widespread use of CHO counting as an effective strategy to promote dietary freedom, quality of life, and glycemic control.

Telemedicine is emerging as a possible solution to support the diabetes patient, to simplify his or her training, and to enlarge the proportion of patients receiving education.[14] A telemedicine system is any technology using telecommunications to support health care (i.e., accurate collection of data in digital format; incorporation of data into an electronic record that may be transmitted with fidelity; protocols for distant analysis; communication tools to permit effective dialogue among primary managers, patients, and consultants).[14] Among telemedicine systems, those based on the use of mobile phones are particularly promising.[15] Hundreds of mobile applications for diabetes are now available to promote self-empowerment or weight loss, to support patient diabetes management, and to remind patients of clinic appointments; however, their efficacy and safety have not been systematically tested or have been tested in studies with methodological flaws.[16–18]

The "Diabetes Interactive Diary" (DID) is a telemedicine system developed in Italy. DID is an automatic CHO/insulin bolus calculator to be installed in the mobile phone. It also works as a communication tool between patient and physician via text messages (short message services [SMSs]). DID has been tested in a process of evaluation similar to that usually adopted for pharmacological products.[19–21] First, its feasibility, acceptability, and safety were documented in a preliminary, pilot study,[20] which involved four diabetes clinics and 50 patients with type 1 diabetes mellitus (T1DM). Second, its effectiveness on metabolic control, weight loss, quality of life, and safety were tested in a randomized clinical trial[21] involving seven diabetes clinics from four countries. The trial involved 120 T1DM patients not previously educated to CHO counting, irrespective of insulin regimen and diabetes duration. The trial compared DID versus standard CHO counting education; it documented a 0.5% reduction in HbA1c levels in both groups, with a halving of the time devoted to education with DID compared with the standard approach. Additional benefits of DID on several generic and diabetes-related scales of quality of life were also found (e.g., treatment satisfaction and perceived frequency of hyperglycemic episodes, as expressed by the Diabetes Treatment Satisfaction Questionnaire [DTSQ][22,23] and Role Physical, General Health, Vitality, and Role Emotional subscales of the 36-item Short Form Health Survey[24]).

Nevertheless, some questions remained open after the trial, particularly related to the effectiveness of DID versus traditional education under routine clinical practice conditions. In fact, standard educational approaches can differ among the different centers according to healthcare operators' attitudes and availability of resources; therefore, the expected benefits of DID in the real world can differ from those that emerged in the previous trial, where CHO counting was taught to all patients. To better reflect the impact of DID in the real world, we also wanted to evaluate the efficacy of DID on metabolic control when all patients are treated with the same insulin regimen and its impact on hypoglycemic episodes, glucose variability, and additional diabetes-specific measures of quality of life investigating social burden, worries, and daily hassles.

These were the objectives of this new confirmatory randomized clinical trial comparing the effects of DID versus usual care in patients with T1DM all treated with the same insulin regimen (basal:bolus of one daily injection of insulin glargine + three injections of insulin glulisine), aiming to complete the existing evidence on efficacy and safety of DID and its potential contribution in simplifying the management of education to patients and healthcare providers if integrated in the usual care.

Patients and Methods

DID system

The DID is a software to be installed in the patient's mobile telephone that works as a CHO/insulin bolus calculator. It supports patients in managing the CHO counting through a food atlas and in recording the self-monitoring blood glucose (SMBG) measurements. On the basis of the stored data (blood glucose values deriving from self-monitoring, individualized correction factor, and insulin:CHO ratio set by the physician, food intake, and physical activities performed), DID automatically calculates the most appropriate insulin dose to be injected at each meal. All the recorded data are sent to the physician on average each 1–3 weeks (depending on the needs of the patient) via SMS and reviewed on the personal computer of the diabetes clinic. Then, any new therapeutic and behavioral prescription can be sent from the diabetes clinic computer to the patient's mobile phone. Further details on the DID features are described elsewhere.[19–21]

Study design and outcomes

This was an open label, multicenter, randomized (1:1), parallel-group study, having as its primary aim the evaluation of the superiority of the DID versus the usual practice in reducing HbA1c levels, when applied in patients treated with

the same insulin regimen (basal:bolus of one daily injection of insulin glargine + three injections of insulin glulisine). Secondary end points were changes in fasting blood glucose levels, glucose variability (expressed as mean amplitude of glucose excursions [MAGE]),[25–27] mean daily doses of basal and prandial insulin, frequency of hypoglycemic episodes, changes in body weight, lipid profile (serum total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglycerides), and blood pressure levels. Finally, quality of life and patient satisfaction were investigated using the DTSQ[22,23] and the Diabetes Specific Quality of Life Scale (DSQOLS).[28–31]

Data were collected at baseline and after 3 and 6 months from the randomization. The study involved 12 Italian diabetes outpatient clinics. The protocol was approved by local Ethics Committees.

Participants

Patients were included if they fulfilled the following inclusion criteria: diagnosis of T1DM, ≥18 years of age, no previous education on CHO counting, HbA1c levels ≥7.5%, treatment with a basal-bolus regimen with insulin analogs, SMBG measurements at least three times a day, and adequate familiarity in the use of mobile phones according to the physician judgment. All the patients were requested to give written informed consent before randomization.

Patients were excluded in case of treatment with NPH insulin or soluble regular insulin, continuous subcutaneous insulin infusion, insulin regimens other than basal:bolus, eating disorders (based on the physician's judgment), pregnancy/lactation, inability to send or receive SMSs, inability or unwillingness to give informed consent, or any other disease or condition that could interfere with the compliance with the protocol or the study completion.

Randomization

Before the start of the study, investigators were involved in a meeting for the standardization of the DID educational training and the definition of criteria for determining the individualized CHO/insulin ratio and the correction factor.[32] These parameters had to be set in the DID for the activation of the bolus calculator.

All recruited patients started (if they did not already use) insulin glulisine as the mealtime rapid analog and insulin glargine as the basal insulin; the pharmaceutical products were provided to the centers by Sanofi-Aventis SpA (Milan, Italy).

Patients were randomized to associate or not the DID system as an aid for CHO counting and the calculation of the most appropriate insulin dose. More specifically, patients were allocated to:

- Group A. Patients were randomized to the experimental group attended a course on the use of DID. The course was provided as an outpatient program of a maximum of three encounters with the physician and/or dietician during a maximum period of 2 weeks. Patients had three prandial injections per day of insulin glulisine associated with basal insulin glargine. Prandial injections could be performed within 15 min before or up to 20 min after the start of the meal, based on the physician's judgment and the patient's needs.[33,34] DID was used to estimate the CHO content of the meal, and prandial insulin doses were adjusted based on the DID algorithm.
- Group B. Patients randomized to the control group received the standard educational approach usually used in the center. The insulin scheme was the same as in Group A. Insulin doses in Group B were adjusted according to the usual practice, on the basis of SMBG values reviewed during the doctor's office visit.

Randomization was performed through a telephone call to the coordinating center. To control for bias deriving from systematical differences in the usual-care approach adopted in the different clinics, random lists were stratified by center. To ensure equal allocation rates within centers, permuted block randomization has been used.

Data collection (Table 1)

At visit −1 (15 days before visit 0), eligibility criteria were verified, a blood sample for HbA1c, fasting blood glucose, and lipid profile measurement was collected, and the patient diary and glucose meter were delivered. The same model of glucose meter (OneTouch® Ultra® 2; LifeScan Inc., Milpitas, CA) was provided to all participants, who were instructed to perform seven-point glucose profiles (before and 2 h after each meal and at 3:00 a.m.) at least three times (two working days and one time during the weekend) during the last 2 weeks before visit 0 and before visit 1 (3 months after randomization). During the last 4 weeks before visit 2 (6 months from randomization), 12 SMBG profiles were requested (i.e., three times a week). Patients received education on hypoglycemia and instructions on how to record on the patient diary throughout the study the results of glucose profiles, daily insulin doses, and hypoglycemic episodes.

Grade 1 hypoglycemia was defined as any symptomatic and/or an asymptomatic fingerstick plasma glucose of <3.3 mmol/L (<60 mg/dL) with the patient not requiring the assistance of other people; grade 2 hypoglycemia was defined as any episode resulting in coma, seizure, or significant neurologic impairment so that the subject was unable to initiate self-treatment or required the assistance of other people.

At study entry (visit 0, randomization), at 3 months (visit 1), and at 6 months (visit 2), clinical information was collected on case report forms. Baseline information included sociodemographic (age, gender, highest level of school education reached, smoking habits) and clinical (diabetes duration, use of SMBG, insulin therapy, presence and severity of diabetes complications, co-morbidities, concomitant treatments) characteristics. HbA1c, fasting blood glucose, blood pressure, and body weight were measured at each visit; lipid profile was measured at baseline and after 6 months. Each of the local laboratories used standard methods to measure these parameters. Furthermore, at each visit, the investigator took off the pages of the patient diary already filled in and attached them to Case report forms.

Patients were requested to fill in the quality of life questionnaires at study entry and 6 months after randomization:

- DSQOLS. The DSQOLS was designed to assess specifically the four main components of quality of life (i.e., physical, emotional, and social burdens along with daily

Table 1. Study Procedures

Visit	*Time*	*Group A (DID)*	*Group B (standard care)*
–1	15 days before randomizzation	• Check of eligibility • Blood sample for HbA1c, fasting blood glucose, and lipid profile • Diary of insulin doses and blood glucose self-monitoring measurements • Prescription of three 7-point glycemic profiles • Instructions for identification, management, and treatment of hypoglycemia	• Check of eligibility • Blood sample for HbA1c, fasting blood glucose, and lipid profile • Diary of insulin doses and blood glucose self-monitoring measurements • Prescription of three 7-point glycemic profiles • Instructions for identification, management, and treatment of hypoglycemia
0	Randomization	• Informed consent • Randomization • Clinical data collection • Download of blood glucose self-monitoring • Diary of insulin doses and blood glucose self-monitoring measurements • QOL questionnaire • Education on DID	• Informed consent • Randomization • Clinical data collection • Download of blood glucose self-monitoring • Diary of insulin doses and blood glucose self-monitoring measurements • QOL questionnaire • Standard education
1	3 months after randomization	• Clinical data collection • Blood sample for HbA1c and fasting glucose • Download of blood glucose self-monitoring and data stored on DID • Diary of insulin doses and blood glucose self-monitoring measurements	• Clinical data collection • Blood sample for HbA1c and fasting glucose • Download of blood glucose self-monitoring • Diary of insulin doses and blood glucose self-monitoring measurements
2	6 months after randomization	• Clinical data collection • Blood sample for HbA1c and fasting glucose • Download of blood glucose self-monitoring and data stored on DID • Diary of insulin doses and blood glucose self-monitoring measurements • QOL questionnaire	• Clinical data collection • Blood sample for HbA1c and fasting glucose • Download of blood glucose self-monitoring • Diary of insulin doses and blood glucose self-monitoring measurements • QOL questionnaire

DID, Diabetes Interactive Diary; HbA1c, hemoglobin A1c; QOL, quality of life.

functioning) in patients with T1DM.[28] After its initial release, the questionnaire was revised to include a new set of questions investigating fears about hypoglycemia. Furthermore, three additional items in the "diet restrictions" scale, two additional items in the "daily hassles" scale, and one item in the "physical complaints" scale were also added.[29] The scale comprises 57 items covering six areas: social relations (11 items), leisure time flexibility (six items), physical complaints (nine items), worries about future (five items), diet restrictions (nine items), daily hassles (six items), and fears about hypoglycemia (11 items). Answers are given on a 6-point Likert scale, and the scores range between 0 and 100, with higher scores indicating better quality of life or higher satisfaction. The translation and cultural adaptation of the Italian version of the instrument were performed using standard forward/backward techniques to ensure conceptual equivalence.[30] The Italian version of the instrument has been extensively validated in a previous study.[31]

- DTSQ. The DTSQ has been specifically designed to measure satisfaction with diabetes treatment regimens.[22] The instrument was originally developed to detect changes in satisfaction related to changes in treatment modalities, but it is also appropriate for comparing levels of satisfaction in subjects using different treatment regimens. It is composed of eight items, six of which are summed in a single score ranging from 0 (very dissatisfied) to 36 (very satisfied). The remaining two items are treated individually and explore the perceived frequency of hyperglycemic and hypoglycemic episodes. The Italian version of the instrument has been previously translated and validated.[23]

Statistical analysis

Sample size was estimated by assuming as clinically relevant between groups a minimum mean difference of 0.5% in HbA1c levels after 6 months, assuming a HbA1c baseline SD of 1.0 (as derived from the previous DID studies). Given these assumptions, 60 patients per group were needed to ensure a statistical power of 80% ($\alpha = 0.05$). The same sample size also allowed detection of a difference between groups of 0.5 SD in MAGE with a statistical power of 80% ($\alpha = 0.05$), assuming an SD of 25% of MAGE, based on the data from the literature.[27–30] Assuming a dropout rate of about 10%, 130 patients were needed.

Baseline patient characteristics according to the randomization arm are expressed as means and their SDs or frequencies. Between-group comparisons are based on the χ^2 test

for categorical variables and the Mann–Whitney test for continuous variables.

Efficacy analyses were based on generalized hierarchical linear regression models for repeated measures.[35] They were applied to assess trends over time between groups. The primary end point was evaluated as the difference between arms at 6 months versus baseline. An unstructured correlation type was used to take into account incomplete follow-up (i.e., dropouts). Because of a between-group imbalance in patient mean age at baseline, this variable was included as a covariate in the regression models. The same method was applied for all the secondary end points. Incidence of grade 1 and grade 2 hypoglycemic episodes was compared between study arms using Poisson regression models. All the analyses were performed on the intention-to-treat population.

Results

Overall, 127 individuals were recruited by 12 diabetes clinics (Fig. 1). Overall, 15 patients dropped out during the study: seven in the standard group and eight in the DID group. Causes of withdrawals are shown in Figure 1. Four patients (two in each arm) dropped out for organizational problems in one diabetes clinic, independently of patients' willingness. No dropout cause was directly related to the DID system or to the insulin treatment. Despite a dropout rate slightly larger than expected (11.8%) and an overall sample of 127 patients instead of 130, the study retained a power of 91% to detect a between group difference of 0.5% in HbA1c levels because the SD of HbA1c at baseline was smaller than hypothesized, being 0.79%.

Patients' characteristics according to the randomization arm are shown in Table 2. The two groups did not differ for any sociodemographic and clinical characteristic, with the exception of a higher mean age in the DID group (38.4 ± 10.3 vs. 34.3 ± 10.0 years; $P = 0.04$). Compared with the standard group, patients in the DID arm also showed a lower frequency of daily SMBG, although statistical significance was not reached.

Between- and within-group changes after 6 months are shown in Table 3. The study failed in demonstrating the superiority of DID compared with the standard care in determining a reduction in HbA1c. In fact, a decrease in HbA1c levels of 0.5% was found in both groups. The between-group comparison in the mean changes of HbA1c levels was not statistically significant, but the improvement in metabolic control was statistically significant and clinically relevant within each group.

The use of DID was associated with a 86% lower risk of grade 2 hypoglycemic episodes compared with the control group (Table 4).

No additional benefits were found on the other clinical secondary end points, such as body weight, fasting blood glucose, lipid profile, and blood pressure. A nonstatistically significant greater reduction in fasting blood glucose was detected in the standard group than in the DID group. Mean daily doses of basal insulin slightly decreased in the DID group (–0.93 ± 0.51 IU) and slightly increased in the control group (0.59 ± 0.50 IU), leading to a statistically significant between-group difference ($P = 0.04$).

The evaluation of MAGE did not show any impact of the DID versus the standard care in reducing glucose variability. However, the compliance with the required frequency of SMBG measurements was low, especially for the nocturnal measurement. Overall, only 31 patients correctly performed all the 18 SMBG profiles requested by the protocol.

The use of DID was associated with improvements in several scales of quality of life: the "perceived frequency of

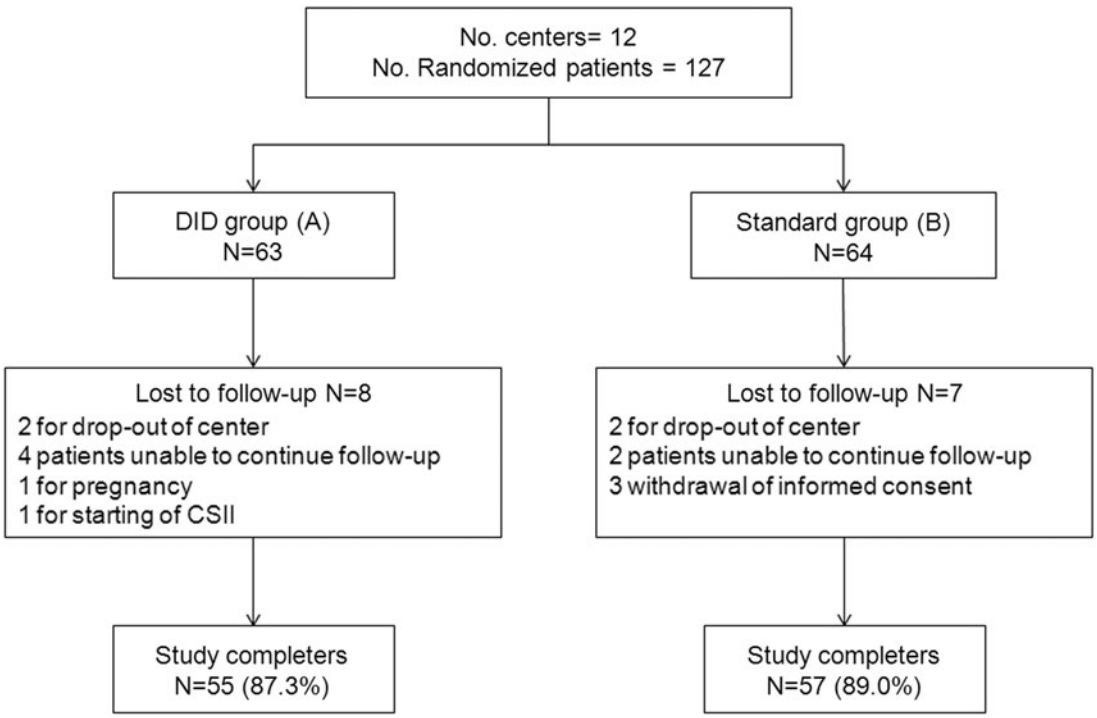

FIG. 1. Study flowchart. CSII, continuous subcutaneous insulin infusion; DID, Diabetes Interactive Diary.

Table 2. Baseline Characteristics According to the Randomization Arm

Characteristic	*DID*	*Standard care*	P[a]
Number of patients	63	64	
Males (%)	46.0	49.1	0.75
Age (years)	38.4 ± 10.3	34.3 ± 10.0	0.04
Highest level of school education completed (%)			
Low level (less than college degree)	15.7	14.8	0.57
Intermediate level (less than university degree)	54.9	66.7	
High level (university degree)	29.4	18.5	
Diabetes duration (years)	16.2 ± 10.0	15.0 ± 8.4	0.73
BMI (kg/m^2)	24.0 ± 3.5	24.8 ± 4.2	0.31
Number of daily blood glucose tests (%)			
3 tests/day	31.4	20.0	0.06
4 tests/day	29.4	50.9	
5 tests/day	31.4	16.4	
>5 tests/day	7.8	12.7	
Short-acting insulin (%)			
Aspart	21.6	20.4	0.83
Lispro	47.1	42.6	
Glulisine	31.4	37.0	
Basal insulin (%)			
Glargine	98.0	100	0.30
Detemir	2.0	0	
Complications (%)			
Retinopathy	15.6	18.7	0.64
Symptomatic neuropathy	1.6	1.6	1.00
Other chronic complications	17.2	15.6	0.81

[a]χ^2 test for categorical variables and Mann–Whitney test for continuous variables.

BMI, body mass index; DID, Diabetes Interactive Diary.

hyperglycemic episodes" dimension of the DTSQ and the "social relations" dimension of the DSQOLS were significantly improved in the DID group compared with the standard group; the "fear of hypoglycemia" dimension improved in the DID group but worsened in the standard group, with a borderline statistically significant difference ($P = 0.06$).

Patients requiring at least one extra visit were 25.0% in the DID group and 31.3% in the control group ($P = 0.43$).

Results obtained with DID markedly differ among patients: the median (minimum; maximum) change was −0.5% (–1.5; +1.3) for HbA1c, 0 (–5; +4) kg for body weight, and +1 (–21; +18) for the DTSQ. The analysis of HbA1c changes according to some key sociodemographic and clinical patient characteristics (i.e., gender, age, and school education) was also performed. The following mean changes of HbA1c after 6 months were documented: −0.64 ± 0.58% in male patients and −0.40 ± 0.61 in female patients ($P = 0.21$); −0.66 ± 0.46 in patients ≤30 years old, −0.39 ± 0.84 in those between 31 and 40 years old, and −0.50 ± 0.54 in those >40 years old ($P = 0.64$); −0.13 ± 0.73 in patients with less than a college degree, −0.57 ± 0.54 in those with less than a university degree, and −0.61 ± 0.60 in those with a university degree ($P = 0.24$); and −0.63 ± 0.54 in patients with diabetes duration ≤10 years, −0.49 ± 0.54 in those with duration between 11 and 20 years, and −0.43 ± 0.68 in those with duration >20 years ($P = 0.65$).

The median number of SMSs exchanged between patient and healthcare professionals also varied markedly, averaging 20 (0; 135). Mean changes in HbA1c according to the number of exchanged SMSs showed the following results: −0.45 ± 0.64% in the subgroup with none to 10 exchanged SMSs, −0.61 ± 0.48 in the subgroup with 11–25 exchanged SMSs, and −0.21 ± 0.71 in the subgroup with 25–135 exchanged SMSs ($P = 0.23$).

The average benefit obtained in the different participating centers varied substantially, with mean HbA1c changes varying from +0.3 ± 0.6% to −1.0 ± 0.4%, mean body weight from +1.7 ± 3.0 to −0.7 ± 1.2 kg, mean number of SMSs exchanged between patient and healthcare professionals ranging between 2 ± 0 and 36 ± 10, and mean DTSQ changes varying from 0.4 ± 4.7 to 9.0 ± 5.2.

Discussion

Among telemedicine systems for mobile phones available today, DID offers the advantage of robust efficacy and safety data deriving from a comprehensive research program including three main studies and subanalyses.[19–21]

Our study confirms previous findings, showing that DID is as effective as the standard educational approach based on CHO counting in improving metabolic control. Although in the previous study patients were treated with any insulin regimen, in the current study all the patients received the same basal:bolus regimen with insulin glargine and insulin glulisine; the effect of DID is thus largely independent of the insulin regimen adopted.

The improvement in metabolic control is obtained while improving quality of life in terms of perception of hyperglycemia, fear of hypoglycemia, and satisfaction with social relations. Improving quality of life and treatment satisfaction represents a key objective of the care of any chronic disease.[6,36] Furthermore, quality of life is widely recognized as an important correlate of adherence to treatment and favorable diabetes outcomes.[37,38] It is thus plausible that the positive impact of DID on several dimensions of quality of life could translate in the long run into better clinical results.

The study adds information on an important effect of DID: its use was associated with a 86% lower risk of grade 2 hypoglycemia than the standard care. This result is particularly valuable, considering the heavy impact of hypoglycemia on clinical outcomes, quality of life,[39,40] and costs of diabetes care.[41]

The study failed to document an effect of DID on the reduction of glucose variability. This should be in part due to the application of the MAGE formula, which today tends to be replaced by other formulas less influenced by the inherent asymmetry of the blood glucose scale (the most indexes are primarily dependent on hyperglycemic blood glucose excursions and generally insensitive to hypoglycemia) and based on a larger number of blood glucose measures deriving from the continuous glucose monitoring.[42,43] In the DID study, a primary problem was the difficulty of the participating patients in recording the seven-point glucose profiles. All required profiles were completed only by one out of four of the recruited patients, and the statistical methods applied could

Table 3. Between- and Within-Group Differences in Clinical Parameters and Quality of Life Scores at Visit 3 with Respect to Baseline Values

	DID group (n = 63)			*Standard group* (n = 64)			P		
	Baseline	*6 months*	*Estimated change*	*Baseline*	*6 months*	*Estimated change*	*Between-group*[a]	*Within DID*[b]	*Within standard*[b]
HbA1c (%)	8.4 ± 0.1	7.9 ± 0.1	−0.49 ± 0.11	8.5 ± 0.1	8.1 ± 0.1	−0.48 ± 0.11	0.73	< 0.0001	< 0.0001
FBG (mg/dL)	186.7 ± 10.1	185.0 ± 8.9	−1.66 ± 12.26	183.2 ± 9.9	150.9 ± 8.3	−32.28 ± 11.76	0.07	0.89	0.01
Blood glucose (mg/dL)									
Preprandial	161.0 ± 4.6	159.6 ± 4.6	−1.42 ± 4.51	162.8 ± 4.6	162.0 ± 4.5	−0.77 ± 4.63	0.91	0.75	0.86
Postprandial	162.9 ± 4.9	168.4 ± 5.2	5.48 ± 4.92	166.9 ± 4.9	169.4 ± 5.1	2.51 ± 4.90	0.91	0.27	0.61
MAGE	128.8 ± 5.9	134.2 ± 6.0	5.36 ± 6.60	132.9 ± 5.9	127.5 ± 5.9	−5.47 ± 6.40	0.24	0.42	0.39
Body weight	68.7 ± 1.8	69.0 ± 1.8	0.38 ± 0.38	70.3 ± 1.7	70.5 ± 1.8	0.28 ± 0.36	0.85	0.32	0.44
Insulin mean daily dose (IU)									
Short-acting	28.3 ± 2.0	27.3 ± 1.8	−0.99 ± 0.93	29.1 ± 1.9	28.9 ± 1.7	−0.23 ± 0.91	0.56	0.29	0.80
Long-acting	20.8 ± 1.4	19.9 ± 1.5	−0.93 ± 0.51	24.0 ± 1.4	24.6 ± 1.4	0.59 ± 0.50	0.04	0.07	0.24
SBP (mm Hg)	119.0 ± 1.4	118.3 ± 1.6	−0.72 ± 1.51	120.0 ± 1.3	118.0 ± 1.6	−2.00 ± 1.45	0.54	0.63	0.17
DBP (mm Hg)	72.9 ± 1.0	72.2 ± 1.0	−2.00 ± 0.94	71.5 ± 1.0	71.7 ± 1.0	0.16 ± 0.91	0.47	0.40	0.86
Total cholesterol (mg/dL)	189.1 ± 3.8	192.8 ± 5.1	3.74 ± 4.36	187.5 ± 3.7	186.9 ± 4.9	−0.63 ± 4.21	0.47	0.39	0.88
HDL-cholesterol (mg/dL)	61.9 ± 2.1	63.0 ± 2.1	1.09 ± 1.60	61.0 ± 2.0	61.3 ± 2.0	0.25 ± 1.57	0.71	0.50	0.87
LDL-cholesterol (mg/dL)	109.4 ± 3.7	117.6 ± 5.3	8.27 ± 4.39	109.1 ± 3.6	114.1 ± 5.2	5.08 ± 4.37	0.61	0.06	0.25
Triglycerides (mg/dL)	83.1 ± 5.6	83.4 ± 5.2	0.39 ± 3.82	86.9 ± 5.5	80.6 ± 5.1	−6.23 ± 3.73	0.22	0.92	0.10
DTSQ									
Score	25.0 ± 0.9	25.9 ± 0.9	0.89 ± 0.89	22.6 ± 0.9	24.6 ± 0.9	1.97 ± 0.88	0.39	0.32	0.03
Hyperglycemia	3.6 ± 0.2	3.0 ± 0.2	−0.53 ± 0.22	3.6 ± 0.2	4.0 ± 0.2	0.39 ± 0.22	0.004	0.02	0.08
Hypoglycemia	3.0 ± 0.2	2.7 ± 0.2	−0.30 ± 0.26	2.6 ± 0.2	2.5 ± 0.2	−0.09 ± 0.25	0.57	0.25	0.71
DSQOLS									
Social relations	79.3 ± 2.1	81.3 ± 2.3	2.00 ± 1.63	85.2 ± 2.1	82.5 ± 2.3	−2.70 ± 1.62	0.04	0.22	0.10
Leisure time flexibility	76.5 ± 2.5	78.0 ± 2.6	1.43 ± 1.82	81.5 ± 2.5	80.1 ± 2.6	−1.35 ± 1.82	0.28	0.43	0.46
Physical complaints	71.0 ± 2.4	73.3 ± 2.6	2.34 ± 1.61	74.8 ± 2.3	75.1 ± 2.6	0.35 ± 1.60	0.38	0.15	0.83
Worries about future	45.0 ± 2.9	47.0 ± 3.0	2.02 ± 2.76	51.8 ± 2.9	52.3 ± 2.9	0.58 ± 2.76	0.71	0.47	0.83
Diet restrictions	61.0 ± 2.9	61.3 ± 2.6	0.32 ± 2.04	64.9 ± 2.8	67.9 ± 2.5	3.07 ± 2.04	0.34	0.87	0.14
Daily hassles	66.3 ± 2.5	64.0 ± 2.7	−2.28 ± 1.92	69.7 ± 2.5	68.3 ± 2.6	−1.32 ± 1.91	0.72	0.24	0.49
Fear of hypoglycemia	65.7 ± 2.6	67.7 ± 3.2	2.03 ± 2.23	70.8 ± 2.6	66.9 ± 3.1	−3.91 ± 2.22	0.06	0.36	0.08
Total burden of diabetes	67.8 ± 1.9	69.1 ± 2.2	1.30 ± 1.36	72.6 ± 1.9	71.7 ± 2.2	−0.91 ± 1.35	0.25	0.34	0.50

Data are mean ± SE values.

DBP, diastolic blood pressure; DSQOLS, Diabetes Specific Quality of Life Scale Questionnaire; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAGE, mean amplitude of glycemic excursions; SBP, systolic blood pressure.

only partly overcome the problem of lack of power on this end point. Further efforts to improve patient compliance with SMBG are therefore strongly needed in order to decrease blood glucose fluctuations, irrespective of the use of telemedicine.

Efficacy, intensity of use, and satisfaction with the DID varied markedly among patients and centers. The greater HbA1c reduction was obtained in younger patients, those of male gender, and those with shorter diabetes duration, although no statistically significant difference was detected.

Table 4. Average Number of Hypoglycemic Episodes per Patient per Year by Randomization Arm and Risk of Hypoglycemia in the Diabetes Interactive Diary Group Compared with the Standard Group

	IR (95% CI)		
Hypoglycemic episodes	*DID group* (n = 63)	*Standard group* (n = 64)	*IRR (95% CI)*
Grade 1	49.2 (46.7–51.9)	45.6 (43.2–48.1)	1.08 (1.00–1.16)
Grade 2	0.33 (0.17–0.63)	2.29 (1.80–2.91)	0.14 (0.07–0.29)

CI, confidence interval; DID, Diabetes Interactive Diary; IR, incidence rate; IRR, incidence rate ratio.

This aspect needs attention. In fact, data on efficacy and safety of technology in diabetes are increasing,[16–18] and new modalities of communication (SMS, e-mail, telephone calls, and other devices) are daily applied by clinicians as surrogates for educational activities to support patients, to reduce the time devoted to education, and to regularly monitor stable patients.[44] Consequently, new policies regulating the execution and the reimbursement of this kind of activities[5] are expected in the next few years. For this reason, the identification of patient characteristics and healthcare professionals attitudes and skills associated with positive results with a care supported by technology will be essential to avoid waste of resources.

No statistically significant correlation was found between number of exchanged SMSs and outcomes. The greater HbA1c reduction was obtained in patients with a number of SMSs exchanged between 11 and 25. The lower decrease in HbA1c levels in those who have had a higher number of SMS exchanges can be explained by the fact that patients with greater problems in managing their disease were more likely to contact the diabetes center.

Furthermore, it is important to underline that the DID system undergoes continuous updates. Now DID is produced as a smartphone application available online for download. In our opinion, more satisfactory results with DID could be obtained by accompanying its technological evolution with a rigorous training to its use, promoting an optimal use also by healthcare operators and patients with a lower attitude to technology. This could be the next challenge for the DID producers.

Our study has limitations. First, expected benefits associated with the use of DID may at least partially depend on the level of education provided by centers. In those centers where education is already provided to the vast majority of patients with high qualitative standards, the gains associated with the use of DID can be less evident. Second, the lack of statistical power limits the evaluation of specific sociodemographic (e.g., gender, age, school education) and clinical characteristics (e.g., diabetes duration, HbA1c levels) correlated to a higher effectiveness of the device. The identification of the subgroups of patients more likely to gain benefits from technology should guide the prescription of the devices in routine clinical practice. Future developments will include the analysis of data deriving from routine clinical practice and to investigate the impact of the system on the different outcomes on a larger sample and in centers and patients using the system according to their own willingness and preferences.

In conclusion, DID is no more effective than traditional education based on CHO counting in reducing HbA1c levels, irrespective of the insulin regimen prescribed to the patient. DID reduces the risk of moderate/severe hypoglycemic episodes and improves several quality of life dimensions. The effect of DID on glucose variability requires further investigation. The prescription of DID and any similar device needs an accurate evaluation of patient attitudes and beliefs, as well as an adequate training of the professionals, in order to exploit all the potential of telemedicine.

Appendix

DID Study Group

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Author Disclosure Statement

G.V. has served as a medical consultant for Me.Te.Da. s.r.l. M.C.R., A.N., G.L., F.P., P.D.B., V.M., and R.A. declare no competing financial interests.

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