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ORIGINAL RESEARCH

Influence of Supervised Disease Understanding and Diabetes Self-Management on Adherence to Oral Glucose-Lowering Treatment in Patients with Type 2 Diabetes

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ABSTRACT

Introduction: Systematic patient education has been reported to improve adherence to treatment, leading to better clinical outcomes. This cluster randomized real-world study investigated the effect of a systematic education program and telephone support on self-reported adherence to oral glucose-lowering treatment in patients with type 2 diabetes mellitus (T2DM).

Methods: Centers were randomized (1:1) to provide either standard-of-care (control group) or standard-of-care along with the education program and telephone support (empowerment group). Adherence to treatment and satisfaction with treatment were assessed using the four-item Morisky Medication Adherence Scale (MMAS-4) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ). The study population included 457 patients (258/199 male/female) with T2DM and non-optimal glycemic control, on oral antidiabetic treatment (age 62.7 [11.4]; disease duration 8.5 [6.5] years).

Results: MMAS-4 high adherence rates for the control and empowerment groups were increased by 3.8% and 16.8% at 4 months

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(Breslow-Day test $p = 0.04$) and by 8.5% and 18.8% at 8 months of follow-up, respectively (Breslow-Day test $p = 0.09$), compared to baseline. Intense physical activity was increased in both control and empowerment groups by 2.3% and 13.9% at 4 months (Breslow-Day test $p = 0.082$) and by 4.0% and 22.5% at 8 months of follow-up (Breslow-Day test $p < 0.001$). Baseline mean (SD) HbA1c was significantly lower in the control group compared with the empowerment group [7.7% versus 8.0%, $p = 0.001$] and decreased in both groups at 4 months by 0.7% and 0.9%, respectively. The change from baseline in the mean DTSQ status score at 4 months was greater in the empowerment group, and the effect was sustained at 8 months (control group: 29.1, 30.5, and 30.9; empowerment group: 25.0, 28.7, and 29.4 at baseline, 4 and 8 months, respectively, $p < 0.001$).

Conclusion: Systematic education combined with telephone support delivered by physicians might be associated with improvement in treatment adherence and treatment satisfaction in patients with T2DM.

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Keywords: Oral glucose-lowering agents; Systematic education program; Telephone support; Treatment adherence; Treatment satisfaction; Type 2 diabetes

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease which is associated with significant premature mortality and morbidity. Diabetes patient care is a complex process, mainly aiming to attain euglycemia with glycated hemoglobin (HbA1c) levels at 7% [1, 2]. Current treatment guidelines encourage healthcare providers and patients to co-develop a "patient-centered" diabetes care plan [2], with the responsibility for the daily self-management activities transferred from the healthcare provider to the patient [3, 4].

National and international diabetes associations recognize patient education delivered in the context of standard care, or in a structured way, as a key component of diabetes care and recommend that it should be provided to all patients [2, 5, 6]. In standard-of-care, patient education comprises basic information on lifestyle modification and disease management. In contrast, structured patient education addresses a multitude of patient characteristics and other factors that influence each person's ability to perform the required self-management activities [6]. Structured patient education can be provided to groups of patients or individually, with each mode having advantages and disadvantages [7–9].

Adherence to the complex T2DM treatment regimen may be overwhelming for patients. In fact, adherence rates have been reported to range from 36% to 93% in patients that remained on treatment with oral glucose-lowering agents for 6–24 months [10]. Adherence to treatment is influenced by a variety of factors, including patient characteristics, characteristics of the treatment regimen, features of the disease, prescriber-level factors (including patient–physician relationship), and the clinical setting [11]. Rubin [12] proposed that "education is a useful resource for addressing all barriers to treatment adherence." Furthermore, the author concluded that self-management education can ultimately lead to improved self-care behavior, glycemic control, and positive patient outcomes.

In Greece, the prevalence of T2DM is estimated at approximately 7.0% [13], and the

prevalence of undiagnosed cases is possibly even higher [14]. The level of diabetes education appears to be poor among patients who are treated with oral glucose-lowering agents [15]. However, Greek patients have been shown to benefit from diabetes education; a relatively recent study reported that a structured 6-h education program delivered in small groups of patients was more effective than standard-of-care in improving glycemic control [16]. Furthermore, a non-experimental study reported that patients adhered to certain aspects of self-management (e.g., diet, blood test exams, regarding self-care etc.) while adherence to exercise and foot management were low [17]. Currently, no studies could be identified assessing the effect of patient education on adherence in Greek patients with T2DM.

This study aimed at evaluating the results of a systematic education program and telephone support on self-reported adherence to treatment with oral glucose-lowering agents in patients with T2DM. In addition, the study sought to investigate the impact of education on other biomedical variables, health-related quality of life, and diabetes treatment satisfaction patient-reported outcomes.

METHODS

Study Design and Participants

ADVICE was a non-interventional, cluster randomized, parallel-group study conducted in 45 primary and secondary outpatient diabetes care centers throughout Greece. Eligible patients were 18 years of age or older, with uncontrolled T2DM (HbA1c $> 7\%$), treated with oral glucose-lowering medications for at least 1 year prior to enrollment. Key exclusion criteria were type 1 diabetes mellitus (T1DM), gestational diabetes, hospitalized patients, and history of alcohol or drug abuse within the year preceding enrolment; pregnant, breastfeeding, or female patients with childbearing potential were also excluded.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013, and with the standards of Good Pharmacoepidemiology Practice; all applicable local laws, rules, and regulations relating to the conduct of the clinical study. Informed consent was obtained from all patients for being included in the study and ethical approval was obtained from all participating centers. Further details regarding the ethics committees from all the participating centers who approved this study can be found in the Supplementary Materials.

Randomization

Randomization took place at center level; centers were randomly assigned (with the use of an electronic algorithm) in a ratio of 1:1 to provide either standard-of-care treatment (control group) or standard-of-care along with a systematic patient education program (empowerment group) to patients with T2DM. Investigators decided independently on the patients' treatment regimen and goals.

In the empowerment group, investigators utilized a sponsor-approved educational material on diabetes which was based on the national and international recommendations. The material included information on disease knowledge, diet and exercise, use of medications and adherence to treatment, adverse events related to treatment, and coping with disease- or treatment-related stress. Investigators were trained on its use for education of their patients during study visits. This material was also provided to patients for further reading following enrollment.

In addition, physicians in the empowerment group were communicating via telephone (approximately bi-weekly) with the patients to support them on the attainment of the treatment goals; predetermined discussion topics included diet, physical activity, adherence to prescribed medication etc. A telephone contact log was used for this purpose.

Procedures

The study follow-up period lasted 8 months. Demographic and biomedical data and patient-

reported outcome questionnaires were collected by the investigators at study entry (baseline visit) and at 4- and at 8-month (± 1 week) visits; the two aforementioned visits were held in the context of standard-of-care. Demographic data included age, gender, age at time of T2DM diagnosis, disease duration (recorded only at baseline), body mass index, waist and hip size, smoking habits, alcohol consumption, and physical activity. Biomedical data included measurements of HbA1c, fasting plasma glucose (FPG), postprandial glucose (PPG), blood lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides), microalbuminuria, blood pressure, heart rate, comorbidities, and preventative screening (lower extremity and eye examinations, and assessment for atherosclerotic cardiovascular disease).

The patient-reported outcomes included in the analysis were adherence to treatment, health-related status, and treatment satisfaction. Adherence to treatment was assessed with the four-item Morisky Medication Adherence Scale (MMAS-4; score range 0–4; higher scores indicate higher adherence) [18]; on the basis of their MMAS-4 score, patients were classified into high, medium, or low adherence (MMAS-4 scores 4, 2–3, and 0–1, respectively). Health-related quality of life was assessed with the five-level EQ-5D (EQ-5D-5L) questionnaire and the visual analogue scale (EQ-VAS) [19]. Finally, treatment satisfaction was assessed with the Diabetes Treatment Satisfaction Questionnaire status (DTSQs; score range 0–36; higher scores indicate higher satisfaction) and change (DTSQc) versions [20, 21].

Objectives

The primary objective was to compare the self-reported adherence to the treatment between the empowerment and control groups, on the basis of the proportions of patients with high versus medium/low self-reported adherence to the treatment at 4 months.

The key secondary objectives included (1) the comparison of the proportion of patients with high versus medium/low adherence to treatment at 8 months between the empowerment control groups and (2) the within-group change in the proportion of patients with high versus medium/low adherence from baseline to 4 and 8 months. Other secondary objectives were the comparison of treatment satisfaction and health-related quality of life status between the empowerment and control groups, at 4 and 8 months; the within-group change of treatment satisfaction and health-related quality of life status from baseline to 4 and 8 months; the comparison of the proportion of patients achieving predefined targets for diabetes, lipid, and blood pressure variables between the empowerment and control groups, at 4 and 8 months. These targets were HbA1c < 7.0%; blood glucose < 110 mg/dl; LDL-C < 100 mg/dl (< 70 mg/dl for patients with diabetes and cardiovascular disease); and systolic blood pressure (SBP) < 130 mmHg (default target for blood pressure, systolic/diastolic blood pressure < 125/75 mmHg in case of renal dysfunction, proteinuria > 1 g/24 h).

Statistical Analysis

The sample size was estimated on the assumptions that among patients with poorly controlled diabetes the proportion of patients with high/medium adherence (defined with MMAS-4) is approximately 60%, the difference in the between-group ratio of patients with high/medium adherence would be at least 15%, and the rate of data loss would be at maximum approximately 10% of the required sample. When a two-sided chi-square test was used with type I error 0.05 and power 0.8, the sample size needed to identify the specified difference between the two proportions was 152 for each group. To account for clustering effects from the randomization scheme, an intraclass correlation coefficient of 0.04 was applied; this increased the sample size to 207 patients. Therefore, the required sample size per arm was 230 patients and the total for both groups was 460 patients with 46 research sites recruiting 10 patients each. This assumption was based on available bibliography data suggesting that the prevalence of self-reported medication nonadherence with the use of MMAS-4 in older adults ranges from 33% to 57% [22–24].

Descriptive analysis was performed to summarize demographic, clinical variables and patient-reported outcomes of study patients. Continuous variables are presented as mean with standard deviation (SD) and categorical variables as counts and proportions.

The association between categorical variables was assessed using the chi-square (χ^2) test. The McNemar test was used for the association of a categorical variable between two time points. Differences of continuous variables at different time points were evaluated with Wilcoxon signed rank test for related samples, while the differences of continuous variables between two groups were evaluated with the *U* Mann–Whitney test for independent samples. The Breslow-Day test for homogeneity of odds ratios was used to compare the change in the rates of high adherence or intense physical activity from baseline to 4 or 8 months.

As a result of the study design, a hierarchical, multilevel, mixed effects model was fitted to further investigate the efficacy of the educational intervention after controlling for baseline differences between the experimental and the control group and for variability in clinical practice among centers. Factors that were associated with a high adherence rate at 4 months ($p < 0.1$) were included in the multivariate model, with random effects fitted for the study centers (further details are included as Supplementary Material).

All statistical tests were two-sided and were performed at a 0.05 significance level. The *p* values were reported, even for non-significant results, rounded to three decimals unless the *p* value was less than 0.001 (in such case $p < 0.001$ was reported). No adjustment for multiple testing was performed. Analysis was performed with SAS® version 9.4.

RESULTS

Patient Demographic and Biomedical Characteristics at Baseline

Forty-five centers were recruited in the study and a total of 457 patients with T2DM were enrolled (Table 1). Female patients accounted for 43.5% of the entire study population. Mean (SD) baseline characteristics were age, 62.7 (11.4) years; duration of diabetes, 8.5 (6.5) years; and HbA1c, 7.8 (0.9) %. Comorbidities and diabetes complications occurred in 75.7% and 7.7% of patients, respectively. The most common comorbidities were arterial hypertension (44.8%), dyslipidemia (39.0%), ischemic heart disease (4.6%), and myocardial infarction (1.7%), while the most common diabetes-related complications were nephropathy (31.4%), retinopathy (25.7%), and neuropathy (17.1%).

Per study design, 23 and 22 centers were randomly assigned to the control and empowerment groups, respectively; as a result of this randomization, 227 and 230 patients were allocated in the control and empowerment patient groups, respectively.

At baseline, certain patient characteristics differed between groups (Table 1). Age and occasional alcohol consumption were significantly ($p = 0.047$ and $p = 0.004$, respectively) higher in the empowerment group, while the use of specific diabetes diet was more common in the control group ($p = 0.028$). Regarding other biomedical characteristics, HbA1c, FPG, and PPG levels were significantly higher in the empowerment versus the control group ($p = 0.001$ for all comparisons; Table 1).

With respect to the patient-reported outcomes at baseline, the MMAS-4 and EQ-5D-5L scores were not statistically different between groups ($p = 0.849$ and $p = 0.376$, respectively; Table 1). In contrast, the EQ-VAS and DTSQs scores were significantly higher for the control versus the empowerment group at baseline ($p < 0.001$ for both comparisons).

Patient Support During Follow-Up Period

Investigators in the empowerment group performed regular (approximately bi-weekly) telephone support sessions with their patients during follow-up. On average, 15.3 (2.8) telephone sessions were performed per patient in this group. The overall frequency of topics discussed during these sessions were diet, 93.0%; physical activity, 88.9%; adherence to

Table 1 Patient characteristics at baseline, overall and per group

	All patients (N = 457)	Control group (n = 227)	Empowerment group (n = 230)	p value
Demographic data				
Age (SD)	62.7 (11.4)	63.8 (10.1)	61.5 (6.7)	0.047
Female (%)	43.5	42.3	44.8	0.591
BMI (kg/m^2)	30.6 (5.3)	30.3 (5.0)	30.8 (5.6)	0.203
Diabetes duration (SD)	8.5 (6.5)	8.8 (6.3)	8.3 (6.7)	0.152
Diabetes history in 1st degree relatives (%)	53.8	54.2	53.5	0.952
Biomedical characteristics				
Comorbidities, all (%)	75.7	78.9	72.6	0.120
Diabetes complications, all (%)	7.7	8.4	7.0	0.570
Physical training				
Intense activity for $\geq$ 20 min, once or more times per week	109 (24.0)	52 (23.0)	57 (24.9)	0.638
No or limited weekly activity	346 (76.0)	174 (77.0)	172 (75.1)	
Patients on specific diabetes diet (%)	47.5	53.7	41.3	0.028
Smoking				0.340
Current	14.4	11.9	17.0	
Former	21.0	22.5	19.6	
Never	61.7	63.4	60.0	
Alcohol consumption				0.004
Daily	4.2	4.0	4.3	
Never	56.9	65.2	48.7	
Occasionally	36.8	29.1	44.3	
Diabetes treatments (%)				
Biguanides	65.9	64.8	67.0	
DPP-4	46.0	43.2	48.7	
SGLT-2	22.8	23.8	21.7	
Insulin (all types)	1.8	0.9	2.6	
HbA1c	7.8 (0.9)	7.7 (0.8)	8.0 (1.0)	0.001
FPG (mg/dl)	149.1 (40.5)	140.9 (31.0)	157.0 (46.6)	0.001
PPG (mg/dl)	175.1 (50.6)	162.1 (30.9)	188.3 (62.2)	0.001
Triglycerides (mg/dl)	162.9 (81.3)	156 (68.3)	169.8 (92.2)	0.446
HDL-C (mg/dl)	45.7 (11.3)	46.4 (10.9)	45.0 (11.7)	0.261

Table 1 continued

	All patients (N = 457)	Control group (n = 227)	Empowerment group (n = 230)	p value
LDL-C (mg/dl)	103.6 (31.6)	100.5 (29.7)	106.6 (33.1)	0.108
TC (mg/dl)	183.3 (36.2)	180.8 (33.6)	185.8 (38.6)	0.159
DBP (mmHg)	79.1 (8.2)	79.5 (8.4)	78.8 (8.0)	0.766
SBP (mmHg)	131.4 (12.9)	132.0 (13.3)	130.9 (12.5)	0.521
Patient-reported outcomes				
MMAS-4 score	3.2 (1.1)	3.2 (1.1)	3.2 (1.0)	0.849
EQ-5D-5L score	0.81 (0.19)	0.82 (0.18)	0.80 (0.20)	0.376
EQ-VAS score	75.8 (16.7)	78.8 (16.1)	72.9 (16.8)	0.000
DTSQs score	27.1 (6.4)	29.1 (6.7)	25.0 (6.7)	0.000

All data are mean (SD) unless otherwise shown. p values are for control versus empowerment group comparison
DBP diastolic blood pressure, *DTSQs* Diabetes Treatment Satisfaction Questionnaire status version, *EQ-5D-5L* EuroQol 5-dimension, 5-level scale, *EQ-VAS* EuroQol visual analogue scale, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *MMAS-4* 4-item Morisky Medication Adherence Scale, *N* total number of patients, *n* number of patients in specified group, *PPG* postprandial glucose, *TC* total cholesterol, *TG* triglycerides, *SD* standard deviation, *SBP* systolic blood pressure

prescribed medication, 81.3%; smoking habits were not a frequent subject of discussion (28.8%).

Improvement in Self-Reported Adherence Rates During Follow-Up

Although the mean baseline MMAS-4 scores were similar between groups, the mean score for the empowerment group was significantly higher compared to control group at 4 months (p = 0.023) and 8 months (p = 0.043) (Fig. 1a).

After controlling for the effect of differences in the clinical practice and baseline covariates, it was observed that the empowerment group was not statistically significantly associated with higher odds of achieving high adherence at 4 months, compared to the control group (OR = 2.1, 95% CI 0.575–7.670; further details are included as Supplementary Material).

For the assessment of the self-reported adherence levels, patients were classified into high (MMAS-4 score 4) or medium/low (MMAS-4 score 0–3) adherence subgroups (Table 2). At baseline, the proportions of patients with high adherence were similar between the control and empowerment groups (57.3% and 53.9%, respectively; p = 0.470). At 4 months (primary objective), the proportion of patients with high adherence was significantly greater in the empowerment than the control group (70.7% versus 61.1%, respectively; p = 0.032; Table 2); compared to baseline, the increase in the proportion of patients with high adherence was significantly greater for the empowerment than the control group (16.8% and 3.8%, respectively; Breslow-Day test p = 0.04; Fig. 1b).

At 8 months, the proportions of patients with high adherence were not significantly different between groups (p = 0.117; Table 2); similarly, the increases in the proportions of patients with high adherence from baseline were non-significant between the empowerment and control groups (18.8% versus 8.5%, respectively; Breslow-Day test p = 0.09; Fig. 1b).

Improvement in Biomedical Characteristics During Follow-Up

Assessment of other biomedical variables is shown in Table 3. Although the mean HbA1c levels were significantly higher for the

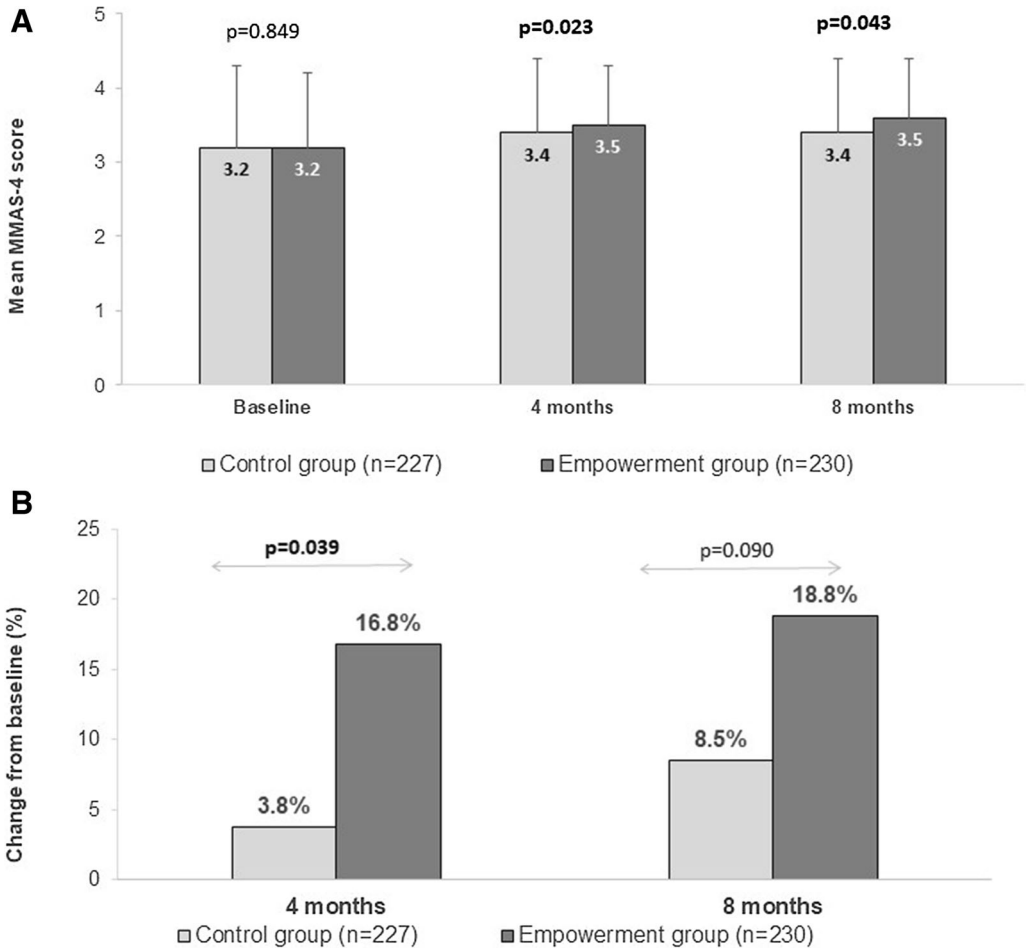

Fig. 1 Per group improvements in self-reported adherence from baseline to 4 or 8 months. **a** Per group improvements in mean MMAS-4 scores from baseline to 4 and 8 months. **b** Per group change in proportion of patients with high adherence from baseline to 4 or 8 months. High adherence was defined as MMAS-4 score of 4. *p* values in **a** are for empowerment versus control group. *p* values in **b** are based on Breslow-Day *t* test for group comparison. *p* values in bold indicate statistical significance. T bars denote the standard deviation

empowerment versus the control group at baseline, the between-group differences at 4 and 8 months were non-significant ($p = 0.724$ and $p = 0.114$, respectively). For the empowerment group, the mean HbA1c was reduced to 7.1% at 4 months (− 0.9% from baseline) and to 7.0% at 8 months (− 1.0% from baseline); for the control group, the respective mean HbA1c levels and reductions from baseline were 7.0% (− 0.7%) and 6.9 (− 0.8%). Similarly, the between-group differences in the levels of PPG and FPG at 4 and 8 months were non-significant, albeit that the respective baseline levels were significantly higher for the empowerment versus the control group. No significant between-group differences were observed in other clinical characteristics such as blood pressure, heart rate, and lipidemic profile at 4 and 8 months.

The rates of intense physical activity (≥ 20 min once or more times per week) were significantly higher in the empowerment group versus the control group at both 4 months ($p = 0.002$) and 8 ($p < 0.001$) months (Table 3); compared to baseline, the increases in the proportions of patients with intense physical activity were significantly higher for the empowerment group compared with the

Table 2 Classification of patients into high or medium/low adherence per group, at baseline, 4 and 8 months

	Control group (n = 227)	Empowerment group (n = 230)	p value
Baseline			
High adherence	130 (57.3)	124 (53.9)	0.470
Medium/low adherence	97 (42.7)	106 (46.1)	
4 months			
High adherence	135 (61.1)	157 (70.7)	0.032
Medium/low adherence	86 (38.9)	65 (29.3)	
8 months			
High adherence	144 (65.8)	157 (72.7)	0.117
Medium/low adherence	75 (34.2)	59 (27.3)	

All data are n (%). Patients were classified into high or medium/low adherence subgroups by means of their baseline MMAS-4 score (high adherence, MMAS-4 score 4; medium/low adherence, MMAS-4 score 0 to < 3). p values are for control versus empowerment group comparison

MMAS-4 four-item Morisky Medication Adherence Scale, n number of patients in specified group

control group at 4 months (13.9% and 2.3%, respectively; Breslow-Day test $p = 0.082$) and 8 months (22.5% and 4%, respectively; Breslow-Day test $p < 0.001$) (Fig. 2).

Improvements in Treatment Satisfaction and Other Patient-Reported Outcomes During Follow-Up

The significantly higher treatment satisfaction levels observed at baseline for the control versus the empowerment group were maintained at 4 months ($p = 0.001$) and 8 months ($p = 0.011$). The mean (SD) change from baseline to 4 and 8 months assessed with the DTSQs questionnaire was significantly ($p < 0.001$) higher for the empowerment versus the control group (Fig. 3).

Compared to baseline, the EQ-5D-5L mean score remained stable for both groups, with no significant between-group differences at 4 months ($p = 0.38$) or 8 months ($p = 0.66$). The significantly lower EQ-VAS mean score for the empowerment versus the control group, observed at baseline, was maintained at 4 months ($p < 0.001$) and 8 months ($p = 0.001$).

DISCUSSION

The ADVICE study assessed the impact of a structured educational program and telephone support on the self-reported adherence to oral glucose-lowering treatment in patients with T2DM. The main finding was that the increase in the proportion of patients with high adherence from baseline to 4 months was significantly ($p = 0.04$) greater for patients who participated in the education program compared with patients who received only standard-of-care. This between-group difference was maintained at 8 months, albeit at not statistically significant levels.

To our knowledge, only a small number of randomized clinical studies have addressed the impact of structured patient education on adherence to treatment. Tan et al. [25] assessed the impact of an education program on adherence to treatment in a population of patients with T1DM and T2DM over 3 months versus standard care. Patients in the intervention group received two individual education sessions followed by a telephone follow-up. The educational intervention focused on self-care practices (including medication adherence) and

Table 3 Development of key biomedical characteristics from baseline through to 4 and 8 months per group

	Patient group		*p* value
	Control group (*n* = 227)	Empowerment group (*n* = 230)	
HbA1c (%)			
Baseline	7.7 (0.8)	8.0 (1.0)	0.001
4 months	7.0 (0.6)	7.1 (0.6)	0.724
8 months	6.9 (0.6)	7.0 (0.6)	0.114
FPG (mg/dl)			
Baseline	140.9 (31.0)	157.0 (46.6)	0.001
4 months	125.7 (21.6)	128.1 (23.5)	0.318
8 months	120.6 (21.6)	123.1 (21.9)	0.294
PPG (mg/dl)			
Baseline	162.1 (30.9)	188.3 (62.2)	0.001
4 months	141.1 (20.4)	154.8 (28.8)	0.001
8 months	141.4 (24.5)	149.2 (24.5)	0.016
TC (mg/dl)			
Baseline	180.8 (33.6)	185.8 (38.6)	0.159
4 months	177.3 (26.3)	178.3 (32.7)	0.769
8 months	172.8 (25.7)	179.7 (32.1)	0.088
TG (mg/dl)			
Baseline	156.0 (68.3)	169.8 (92.2)	0.446
4 months	140.2 (45.8)	148.4 (61.4)	0.362
8 months	137.1 (47.6)	144.4 (60.6)	0.271
HDL-C (mg/dl)			
Baseline	46.4 (10.9)	45.0 (11.7)	0.261
4 months	47.7 (10.2)	47.2 (11.7)	0.643
8 months	47.6 (9.8)	47.2 (10.8)	0.726
LDL-C (mg/dl)			
Baseline	100.5 (29.7)	106.6 (33.1)	0.108
4 months	100.0 (25.1)	97.9 (28.5)	0.365
8 months	94.8 (26.3)	101.1 (30.1)	0.183
DBP (mmHg)			
Baseline	79.5 (8.4)	78.8 (8.0)	0.766
4 months	78.9 (7.7)	78.2 (7.2)	0.301
8 months	78.3 (7.2)	78.5 (7.9)	0.740
SBP (mmHg)			
Baseline	132.0 (13.3)	130.9 (12.5)	0.521
4 months	129.6 (12.1)	128.3 (10.7)	0.708
8 months	129.7 (12.4)	129.0 (10.7)	0.778
Intense physical activity, *n* (%)			
Baseline	52 (23.0)	57 (24.9)	0.638
4 months	56 (25.2)	86 (38.7)	0.002
8 months	59 (26.9)	103 (47.2)	< 0.001

All data are mean (SD) unless otherwise shown. *p* values are for the control versus the empowerment group comparison

DBP diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *n* number of patients in specified group, *PPG* postprandial glucose, *TC* total cholesterol, *TG* triglycerides, *SD* standard deviation, *SBP* systolic blood pressure

problem-solving skills. Consistent with the main findings of this study, it was reported that patients in the intervention group presented significantly higher adherence rates than patients in the control group, with a greater improvement in adherence rates from baseline. Other randomized clinical studies have also reported that diabetes education improves adherence to treatment in the short term (≤ 6 months) in patients with T2DM [26–29]. It is unclear whether this favorable impact of education on adherence to treatment is sustained in the long term.

With respect to glycemic control, the present study shows that both groups attained similar mean HbA1c levels at 4 and 8 months. As already stated, the HbA1c levels at baseline,

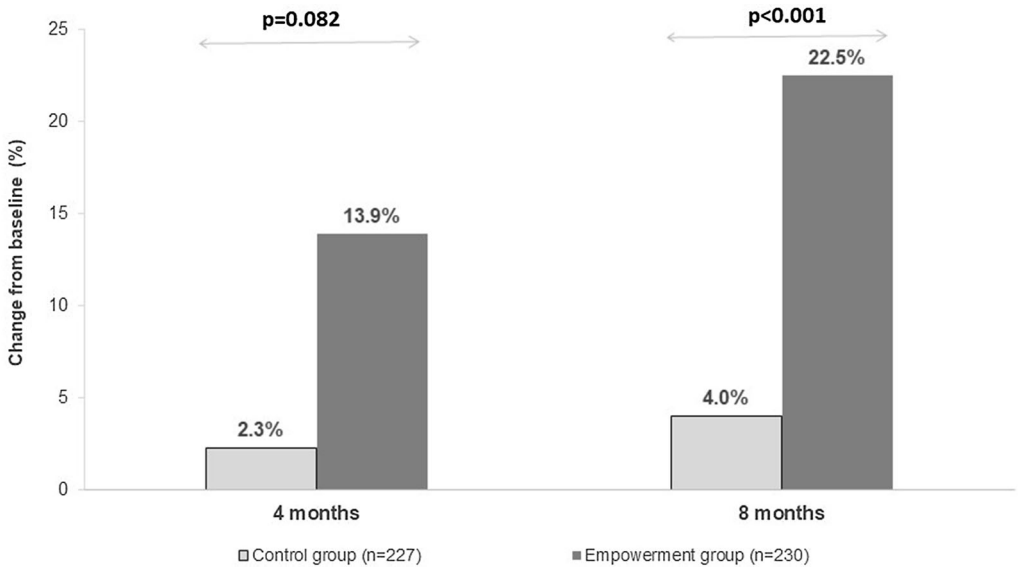

Fig. 2 Per group change in the proportion of patients with intense physical activity (defined as ≥ 20 min once or more times per week) from baseline to 4 or 8 months. *p* values are based on Breslow-Day *t* test for group comparison

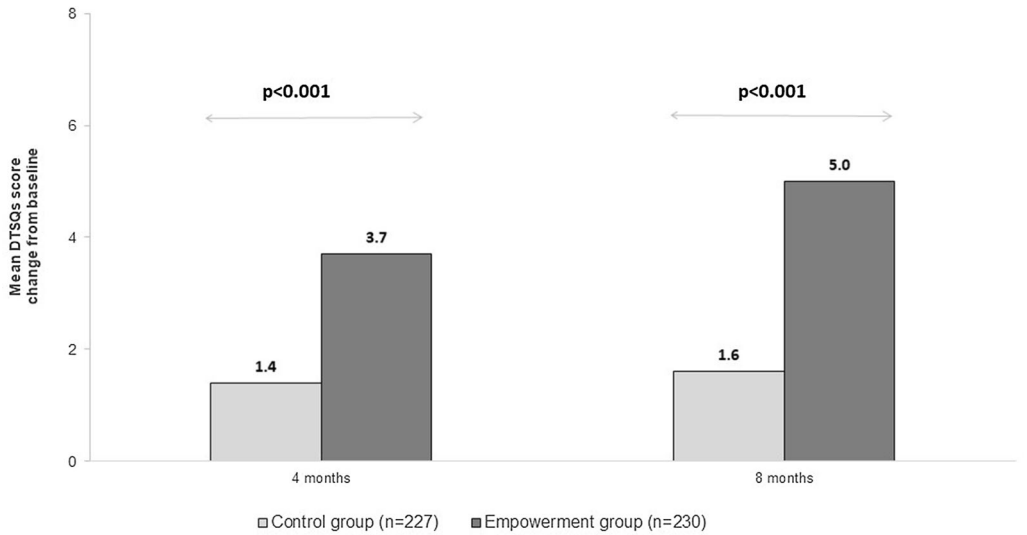

Fig. 3 Per group change in treatment satisfaction from baseline to 4 or 8 months. DTSQs Diabetes Treatment Satisfaction Questionnaire status. *p* values are for empowerment versus control group

along with other variables such as age and alcohol consumption, were significantly lower versus the empowerment group; this difference may have masked any comparative effectiveness of the educational program on glycemic control. Previous studies have shown that face-to-face education (the delivery mode used in the present study) was significantly more effective in the reduction of HbA1c levels and other diabetes-related biomedical characteristics compared with standard-of-care [30–32]. On the contrary, telephone contacts as a means of reinforcement of a previous educational program do not appear to have an additional effect on the HbA1c levels [33]. With respect to the long-term maintenance of glycemic control, Khunti et al. [34] reported that most of the improvements seen at 12 months in HbA1c

levels were not sustained after 3 years. Clearly, the evaluation of the long-term effect of education on adherence to treatment would be an interesting research topic for future trials.

Another finding of the present study was the significant increase in the proportion of patients in the empowerment group performing intense physical activity at 8 months versus those in the control group. Physical activity is a key constituent of diabetes management as it contributes to improved glycemic control [35]. A recent study assessing the impact of education on perceived benefits, barriers, and self-efficacy reported significant improvements in the mean metabolic equivalent of task in the intervention versus the control group [36]. In the present study, this increase in physical activity did not appear to translate into biochemical improvements; however, it is considered that there may be a lag effect and therefore potential improvements would have been apparent beyond 8 months.

Finally, regarding treatment satisfaction, patients in the empowerment group had a significantly lower DTSQs score at baseline versus patients in the control group. As treatment satisfaction is inversely related to HbA1c levels [37], it is possible that the observed difference in satisfaction levels at baseline may be related to the significantly higher HbA1c levels of the empowerment group. As already stated, the significant difference of the control versus the empowerment group persisted throughout the observation period. Despite this, the change from baseline to 4 or 8 months in terms of treatment satisfaction was significantly higher for the empowerment versus the control group. This finding concurs with the findings of the BENCH-D study [38], which showed that higher empowerment levels in patients with T2DM were associated with improved treatment satisfaction. The results regarding the quality of life are presented with caution, since the statistically significant difference of EQ-5D VAS might depict the baseline differences between the two groups.

The present study has several limitations. Physicians in the control group may have inadvertently treated their patients in a more than standard-of-care manner with regards to providing relevant information. Despite study protocol clarity, variability in participating physicians' practices, measurements, and delivery of education cannot be ruled out. Selection bias cannot be ruled out with respect to participating centers.

It is possible that the differences in key diabetes variables (HbA1c, FPG, and PPG) at baseline between patients allocated in the empowerment and control groups may have masked the impact of education on these variables. However this study design implies that the empowerment and the control groups may differ in terms of baseline characteristics, and thus this was an expected study feature that was further evaluated using a multilevel mixed model analytical approach. After taking into consideration the variation of clinical practices between the participating sites and baseline covariates, the multivariate analysis showed that the empowerment group was not statistically significantly associated with higher odds of achieving high adherence at 4 months, compared to the control group, even though the estimate of the OR remained favorable for the empowerment group (OR 2.1, 95% CI 0.575–7.670).

CONCLUSIONS

This cluster randomized real-world study provides evidence that a structured educational program may lead to improved short-term adherence to treatment in patients with T2DM. Patients who participated in the educational program experienced greater treatment satisfaction and increased their physical activity levels compared with patients receiving standard care.

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committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013, and with the standards of Good Pharmacoepidemiology Practice; all applicable local laws, rules, and regulations relating to the conduct of the clinical study. Informed consent was obtained from all patients for being included in the study and ethical approval was obtained from all participating centers. Further details regarding the ethics committees from all the participating centers who approved this study can be found in the Supplementary Materials.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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