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ORIGINAL ARTICLE

A randomized controlled trial comparing a telemedicine therapeutic intervention with routine care in adults with type 1 diabetes mellitus treated by insulin pumps

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Abstract

Aim To examine the effectiveness and safety over a 12-month period of a telemedicine intervention in adults with type 1 diabetes (T1D) treated with insulin pumps.

Methods 74 T1D patients on insulin pumps for at least 1 year (mean 19.5 [11.5] years) and $HbA1_c \geq 6.5\%$ (≥ 48 mmol/mol) were randomized to the telemedicine ($n = 37$) or the standard care group ($n = 37$). The intervention group was instructed to download data from insulin pumps and glucometers monthly. They received immediate phone feedback and recommendations for insulin dose adjustment; and face-to-face visits once in 6 months, compared to once every 3 months for the standard care group. Satisfaction with treatment, quality of life and frequency of hypoglycemic events was evaluated.

Results The mean changes in HbA1c adjusted to baseline were −0.08% (0.25 mmol/mol) vs. −0.01% (0.03 mmol/mol), in the intervention and control groups, respectively ($p = 0.18$) at 12 months, without an increased frequency of hypoglycemia. Patients in the intervention group felt satisfied and interested in continuing with the treatment ($p = 0.04$). The quality of life scores were similar in both groups. Direct total costs were 24% less in the intervention group, and indirect total costs decreased by 22% compared to the year preceding the study.

Conclusions Internet-based insulin dose adjustment is as effective and safe as routine care in adults with type 1 diabetes treated by insulin pumps. For suitable patients, some of the time-consuming routine visits may be replaced by user-friendly digital medicine.

Clinical trial registration Clinical Trial.gov Identifier NCT01887431.

Keywords Internet-based therapeutic intervention · Telemedicine · Type 1 diabetes mellitus · Young adults

Introduction

Advances in modern technology in recent years have transformed the classical way of delivering healthcare services. Wide-scale exchange of medical information via electronic communication has demonstrated improvement in patients' health status [1–3], particularly by increasing patient and care provider interaction [4].

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The Diabetes Control and Complications Trial emphasized the importance of frequent visits in the intensive therapy group, thus demonstrating that close information exchange with proper feedback is basic in lowering $HbA1_c$ and in reducing long-term diabetes complications [5]. Despite data supporting a favorable impact of intensive care on life expectancy and healthcare costs [6], and no deterioration in quality of life (QoL) outcomes [7], the realization of such in daily clinical practice can be difficult. Telemedicine seems a feasible and suitable way to achieve therapeutic goals of type 1 diabetes (T1D).

Studies of telemedicine in adults with T1D showed equivalent $HbA1_c$ improvement in both intervention and control groups [8]. However, these studies are limited by their investigation of heterogeneous populations, their use of less sophisticated technologies than are currently available, and only a few reported patient costs [9, 10]. In addition, some only involved data transfer and not active feedback. Therefore, we conducted a randomized clinical trial for 12 months to examine the effectiveness, safety, acceptability to patients, and cost-effectiveness of telemedicine, compared to standard care treatment of T1D in adults using insulin pumps.

Methods

The trial was conducted in a referral center for T1D in the Maccabi Heath Care Services, the second largest healthcare provider in Israel. Study inclusion criteria were: aged > 22 years, diagnosis of T1D at least 1 year, and treatment by an insulin pump for at least 6 months. Exclusion criteria included pregnancy, history of severe target organ damage, eating disorders, mental disabilities, and a clinical condition requiring the patient to receive follow-up more frequently than the half-year visits scheduled in the intervention. All participants provided written consent and local ethics committee approved the study. **ClinicalTrial.gov Identifier**: NCT01887431.

Trial design

This 12-month open-label randomized (1:1) controlled trial was designed to evaluate whether the use of the telemedicine improved $HbA1_c$. Pre-specified secondary outcomes included changes in QoL score, treatment satisfaction (DTSQ) score, changes in total hypoglycemic events (defined as blood glucose [BG] ≤ 70 mg/dl) and hyperglycemic events (defined as BG ≥ 300 mg/dl). The cost-effectiveness of the intervention was evaluated. Protocol and study timeline are attached in online supplementary resources Table S1 and Figure S1.

All patients used Medtronic MINIMED™ PARADIGM™ VEO™ insulin pumps and were instructed to maintain their routine self-monitoring of BG (SMBG) using FreeStyle lite glucometers at least four times a day. Patients in the intervention group were instructed to download data from the insulin pump and glucometer once a month from 14 days prior to the transfer and to transmit this information to the clinic by Carelink Pro Software (https://www.professional.medtronicdiabetes.com/carelink-system). Physicians reviewed the data and immediately documented the recommendations. The study coordinator informed the patients about updated recommendations by phone feedback calls within 72 h after transmission. The recommendations included instruction on how or whether to adjust insulin doses and motivational support. In addition, patients had face-to-face visits with a physician once in 6 months (3 visits in 12 months), instead of the 3-month interval follow-up visits generally scheduled in the clinic.

Patients in the standard care group did not submit web results, kept routine follow-up visits at 3-month intervals (a total of 5 visits in 12 months), and received conventional treatment that was based on data from 14 days prior to the face-to-face visit downloaded at the clinic. Routine care was defined by current ADA guidelines [11] and local Disease Management Programs for T1D in Israel [12]. At each face-to-face visit for both groups, compliance with SMBG and wizard bolus use was assessed. The duration of the visits was identical for both groups and recommendations were reviewed during the next visit. After randomization, only insulin dose adjustment and carbohydrate counseling were permitted. All participants could make urgent phone calls and e-mail contacts to physicians, dietitians, or secretary of the department, as part of routine care in our department.

The safety variable was comprised of: (1) severe hypoglycemic episodes, defined as events requiring third-party assistance, (2) symptomatic and asymptomatic hypoglycemic events ≤ 70 mg/dl, and (3) hyperglycemic events ≥ 300 mg/dl recorded by both groups from the 14 days SMBG personal diary prior to each visit.

After a 2-week run-in period, eligible patients were randomly assigned and stratified by values of $HbA1_c$ (< 7.5%, ≥ 7.5%) to the intervention and control groups. To evaluate the time spent by staff in the delivery of care to patients, we recorded the duration of face-to-face visits in both groups and the duration of tele-consultations in the intervention group; the latter comprised physician time spent for transmitted data evaluation, typing recommendations and the time spent by the study coordinator in the phone call that provided feedback.

Health-related quality of life measures

Changes from baseline in satisfaction in diabetes treatment and health-related QoL were evaluated using the Hebrew version of the DTSQs and DTSQc change version

(DTSQc) [13] and the Audit of Diabetes Dependent Quality of Life 19 questionnaire (ADDQoL) questionnaires. DTSQ evaluates satisfaction with the diabetes treatment regimen and is composed of eight items, six of which are summed into a single score on a 7-point scale, ranging from very satisfied to very dissatisfied. The remaining two items are treated individually and explore the perceived frequency of hyperglycemic and hypoglycemic episodes. The DTSQc compares the experience of the current treatment to the experience of the treatment before the study. Scores range from + 3 ("much more satisfied now") to − 3 ("much less satisfied now"), with 0 (midpoint), representing no change. The ADDQL originally presented in [14] and was later modified in [15] and consists of 19 questions on QoL with diabetes. The DTSQs and ADDQL were administered at baseline, and at 6 and 12 months, and the DTSQc at 12 months.

Cost-effectiveness analysis

A cost analysis was performed from Maccabi Heath Care Services database [16] to determine direct medical expenses, which comprised costs to the payer and insurance company for the clinical visits, and additional costs to the patients for travel expenses (parking, mileage) in both groups. Costs in the intervention group included time spent on instruction using telemedicine, education to download the data and transmission, and time the physician and dietitian spent in reviewing data, documenting recommendations and providing feedback to patients, including calls that were not answered. The costs of the transmissions and face-to-face visits were calculated according to hourly wages ($40 for nurse, $38 for social worker, $33 for dietitian, and $75 for physician). Costs per patient as a payer were analyzed according to patient time for the face-to-face visits and the time required for downloading and transmission of data calculated according to the average Israeli salary in 2016, net 9904 New Israeli Shekels (NIS) [2815 US$], gross 12 560 NIS [3570 US$] for an employee, and a cost of $15.00/h on the basis of 186 monthly working hours.

Indirect costs were calculated as the sum of pharmaceutical costs, laboratory costs, hospital expenses, clinical visits other than to the diabetes clinic during the year preceding entry to the study, during the 12-month study period, and during the 1 year after the study. Expenses were calculated for each individual directly from the patient administration system, to examine a possible financial impact of the study on insurance company expenses. The average time of workloss per year was estimated; other indirect costs such as productivity losses due to sick leave and early retirement are not included. We compared direct and indirect total costs of the control and intervention groups after 1 year of the study.

Statistical analysis

The sample size was calculated under the assumption that the difference in the mean change in HbA1c between treatment groups would be 0.5% with a standard deviation of 0.7; in this case a sample size of 31 in each group was required for a power of 80%. We aimed to recruit 70 patients for randomization into treatment groups, assuming that 10% would not complete the study. Efficacy outcomes were analyzed on an intention-to-treat basis. Missing data were imputed with the last observation carried forward (LOCF) method.

Categorical and binary data were expressed as frequencies and percentages; quantitative data were expressed as mean values and standard deviation, with and without adjustment for baseline values. Proportions were compared using Chi square or Fisher's exact test as appropriate. Continuous variables were compared between groups using a *t* tests, when the distribution assumption was appropriate for the data or the rank-sum Wilcoxon test, as appropriate.

A multivariate linear regression was performed to test the effect of the treatment groups on changes in HbA1c, adjusted for gender, age, disease duration and baseline values of $HbA1_c$. Statistical analyses were performed using the SAS for Windows, version 9.2.

Results

From December 15, 2013 to November 30, 2015, a total of 67 (91.8%) patients with T1D who were treated with insulin pumps, 31 in the intervention group and 36 in the standard treatment group, were included in the final analysis (Figure S2). Patient characteristics are shown in Table 1. The two groups did not differ in any of the sociodemographic or clinical characteristics examined, with the exception of a non-significantly higher baseline level of HbA1c in the control group.

Glycemic control

At baseline, the mean (SD) $HbA1_c$ was 7.59% (0.82%), [59 (2.46) mmol/mol], in the intervention group and 7.93% (0.69%), [63 (2.01) mmol/mol] in the control group ($p = 0.07$).

After 52 weeks, the mean HbA_{1c} levels were 7.52% (0.62%), [59 (2.0) mmol/mol] in the intervention group and 7.92% (0.83%), [63 (2.46) mmol/mol] in the control group. The mean adjusted to baseline was similar, 7.50% (0.57), in the intervention group and 7.92% (0.48) in the control group. The mean (SD) change in HbA_{1c}, adjusted to baseline, was not significantly different in the intervention than the control group: − 0.08% (0.25%) vs. − 0.01% (0.03%) ($p = 0.18$) (Fig. 1). Subsequently, multivariate

Table 1 Baseline demographic and clinical characteristics of Type 1 diabetes patients assigned to the intervention and control groups

Variable	Intervention group ($n=31$)	Control group ($n=36$)
Age, years	43 (11)	45 (14)
Range	26–68	25–73
Diabetes duration, years	23 (10)	24 (13)
Range	5–38	5–52
Gender, M/F	19/12	13/23
BMI, kg/m^2	26.6 (4.6)	25.5 (3.8)
HbA1$_c$ value*		
% (mmol/mol)	7.59 (0.82)	7.93 (0.69)
	59 (2.46)	63 (2.01)
≥ 8% (63.9 mmol/mol)	13 (42%)	15 (42%)
Hypertension (%)	27	25
Hyperlipidemia (%)	26	22
Smoking (%)	16	19

Data are mean values (± standard deviation), unless stated otherwise

BMI Body Mass Index, *HbA1$_C$* glycated hemoglobin

models were applied after adjusting for other demographic and medical variables of interest (gender, age and duration of diabetes), as well as baseline HbA1$_c$; and yielded similar results (Table 2).

The frequency of hypoglycemic events retrieved from SMBG reports that included documented symptomatic hypoglycemic episodes reported by participants did not differ significantly between the groups at baseline and at the end of the study (Table 3). One participant in the intervention group experienced a severe hypoglycemic episode in the 9th month of the study. Neither frequency of hyperglycemia episodes ≥ 300 mg/dl, nor the incidence of diabetic ketoacidosis differed significantly between the groups (Table 3).

The proportions of participants that achieved or maintained the target HbA1$_c$ ≤ 7% at the end of the study were 13.33% ($n=4$) in the intervention and 5.56% ($n=2$) in the control group ($p=0.39$).

Table 2 Linear regression analysis for change in HbA1c, with imputation of missing data

Dependent variable	Continuous delta		
	Parameter	SE	*P* value
Treatment group	− 0.141	0.143	0.33
HbA1$_c$ at baseline	− 0.290	0.092	0.003
Gender	− 0.066	0.145	0.65
Age	0.008	0.006	0.19
Disease duration	0.000	0.007	0.99

P values were calculated using *t*-test for continuous variables

HbA1c glycated hemoglobin, *SE* standard error

Table 3 Documented hypoglycemia (symptomatic and asymptomatic) and hyperglycemia events

Number of hypoglycemia ≤ 70 mg/dl	Intervention ($n=31$)	Control ($n=36$)	*P* value
Baseline	5.68 (6.16)	4.92 (5.27)	0.59*
At week 52	5.16 (5.51)	5.39 (5.09)	0.86**
Number of hyperglycemia ≥ 300 mg/dl			
Baseline	2.74 (3.73)	3.83 (3.28)	0.21*
At week 52	2.90 (3.79)	4.00 (4.79)	0.31**

Data are mean values (SD) expressing number of hypoglycemic and hyperglycemic events in the 14 days per each patient

P values were calculated using *t* test

**p* values for the difference between the groups at baseline

***p* values for the difference between the groups at 52 weeks

Quality of life and patient satisfaction

After 52 weeks, patient satisfaction with their diabetes treatment was high in both study groups; the intervention group stated "much more satisfaction" for continuing with

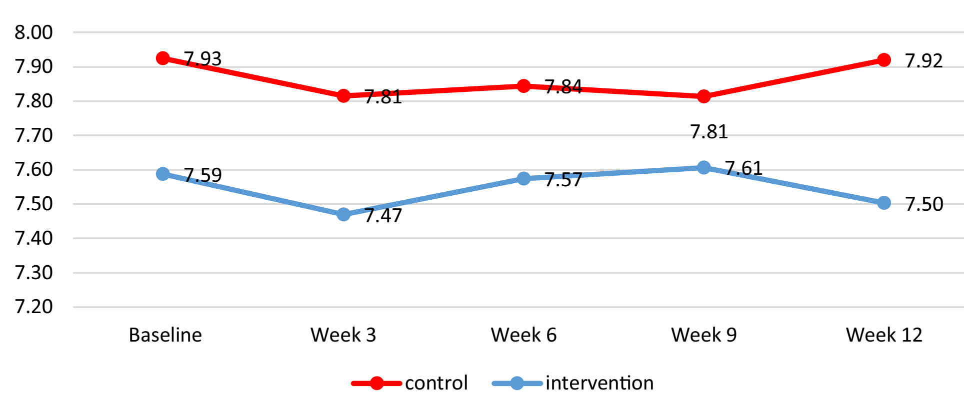

Fig. 1 Mean HbA1$_c$ levels at baseline and after 3, 6, 9, and 12 months. Adjusted changes at 6 months: − 0.01% in the intervention group (blue line), − 0.08% in the control group (red line) ($p=0.77$); at 12 months − 0.08% (0.25 mmol/mol) in the intervention group, − 0.01% (0.03 mmol/mol) in the control group ($p=0.18$). HbA1$_C$, glycated hemoglobin

the telemedicine intervention than did the control group: + 2.1 [1.21] vs. +1.4 [1.35], $p = 0.04$ (Table S2).

QoL was similar between the groups at baseline and at the end of the study. After 52 weeks, only 6% of the participants stated that diabetes had a negative impact on their QoL, while 83% believed that their life would have been better without the presence of diabetes, although the differences in QoL between the groups were not significant.

Cost-effectiveness analysis

Physicians spent a mean 4.6 min per transmission reviewing the data and documenting recommendations. The study coordinator spent a mean 3.4 min per contact providing feedback to patients, for a mean 7.8 transmissions per participant in the 12 months of study. The numbers of transmissions sent were fewer than the 12 anticipated. Direct costs per patient for the intervention and standard care groups are compared in Table 4.

Direct total costs were greater by 24% in the control than in the intervention group after 1 year of the study. The mean annual direct costs related to diabetes were estimated at $546 in the control group vs. $428 in the intervention group for the insurance company (22% difference); and $190 in the control group vs. $132 in the intervention group per patient as a payer (33% difference). Forty percent less time was spent at face-to-face visits for participants in the intervention than the control group: 3 vs. 5 visits. This resulted in savings for the payer and the insurance company.

Lastly, total annual indirect medical expenses decreased in the intervention group by 22% compared to the year preceding the study, while in the controlled group the expenses changed minimally and decreased by 4% (Table S3).

Discussion

During the 1-year course of implementation of a telemedicine intervention in adults with T1D treated by insulin pumps, glycemic control was maintained, with a trend toward improvement. Although statistically significant improvement in glycemic control was not reached, quality of life remained, satisfaction increased to a greater degree in certain parameters, and safety was well maintained. Furthermore, the direct cost of care was reduced by one-third, and calculated expenses decreased by 22% compared to the year preceding the study.

Due to its feasibility and accessibility, telemedicine is common in diabetes management [8, 17]; although long-term evidence is scarce. Scant improvement in glycemic control was shown after short-term intervention. In one of the first randomized telemedicine intervention studies, conducted among poorly controlled adolescents with T1D, Chase et al. [18] did not find a difference in glycemic control after 6 months of the intervention, between those who used a BG transmission modem and phone feedback and those treated by standard care. They concluded that telemedicine as a means of diabetes care is appropriate but obviously not suitable for all families and adolescents, especially not for those with noncompliance or psychological issues or those needing further diabetes education. Shortly thereafter, Montori et al. [19] published data of a 6-month telemedicine

Table 4 Direct expenses ($) to the insurance company and to the patients

Per insurance company	Intervention group ($) [min]	Control group ($) [min]	Difference cost (I-C) (%)
Time for instruction using telemedicine	4 [5]	0	4
Physician's wage	175 [141]	217 [175]	-42
Nurse's wage	70 [105]	116 [175]	-46
Dietitian's wage	74 [131]	99 [175]	-25
Social worker's wage	68 [105]	114 [175]	-45
Modem cost wage	37		37
Subtotal per insurance company	428	546	− 118 (− 22)
Per patient as a payer			
Instruction/transmission time	2 [2]/7 [5]		10
Time spent on face-to-face visits	78 [131]	122 [175]	-44
Time spent on phone with study coordinator	8 [26.5]		8
Travel mileage/parking expenses	17 [105]/20	28 [175]/40	− 11/− 15
Subtotal per payer	132	190	− 58 (− 33)
Total direct costs for the payer and the insurance company	560	736	− 176 (− 24)

intervention of poorly controlled adults with T1D (baseline $HbA1_c$ 8.9% [1.27%]) and showed only slight improvement in glucose control, as assessed by $HbA1_c$. Even a complex educational approach in telemedicine, which included carbohydrate counting, as in the DID study, did not notably affect glycemic control [20]. On the other hand, a later trial, which used more advanced technology and sophisticated software showed improved glycemic control in poorly controlled T1D patients when teleconsultations were frequent and included SMBG, diet and insulin treatment data [21]. Likewise, a pooled analysis and meta-analysis of randomized controlled studies [3] showed a positive trend of telemedicine intervention on glycemic control; however, the mean reduction in $HbA1_c$ level was marginal and the cost-effectiveness evaluated in a few studies was generally questioned and showed small benefit [8, 21].

Similar to previous randomized short-term studies, our 1-year study involved SMBG, insulin pump data transmissions, insulin dose adjustment and a carbohydrate calculation intervention if needed. Concurring with the results of those studies, the current study did not demonstrate a superiority of telemedicine in regard to glycemic control after 1-year of the intervention, but long-term safety and non-inferiority of glycemic status were shown. Specifically, $HbA1_c$ was reduced slightly compared to standard care, without increased frequency of hypoglycemia. In addition, patients in the intervention group expressed interest in continuing treatment by telemedicine, and would recommend this approach to their peers. They did not find the frequent phone contracts and teleconsultation as an inconvenience. In accordance with our findings, a recently published study conducted on adults with T1D, 45% of them treated by insulin pumps [22], reported no statistically significant change in $HbA1_c$ level in a teleconsultation intervention group, despite intensive web-based care including video communication, educational courses and nutritional and psychological counseling.

The results of the direct cost-effectiveness analysis presented herein are encouraging. The intervention group saved almost half of the face-to-face visit time and one-third of direct cost expenses. The importance is very high as diabetes is one of the most common chronic diseases. Costs of related healthcare are expected to rise dramatically, from approximately 10% of the current total health resource expenditure, to double the amount in 20 years [23].

The question remains as to why the convenient, feasible and highly acceptable therapeutic approach of telemedicine was not more effective in improving glycemic control in this and other studies. For one, the participants received frequent education and support before study enrollment; and their glycemic control was reasonable. Therefore, we recognized that achievement of further reduction in $HbA1_c$ levels would be hard. Second, the evaluation of a single glycemic control parameter may not reflect all the benefits of the telemedicine intervention and other modalities such as time spent in the target blood glucose range and an area under the curve analysis attained from continuous glucose monitoring could contribute to more precise evaluation of the intervention's effectiveness. The lower frequency of face-to-face visits in the telemedicine group may have decreased the positive outcome of the intervention. However, the lower frequency of face-to-face visits is integral to the telemedicine approach, so distinguishing its effect may not be relevant.

Several limitations of this study warrant consideration. First, due to patient withdrawal from the study, the number of subjects included in the final analysis was eventually lower than planned. Second, although the frequency of hypoglycemic events retrieved from SMBG did not significantly differ between the groups, we did not have data from continuous glucose monitoring (CGM), which may have revealed asymptomatic hypoglycemic events. Finally, we did not evaluate indirect cost-analysis data that comprises a considerable portion of the expenses; this would mostly be due to loss of individual working productivity. Improvements in diabetes treatment may lead to better glycemic control and fewer complications, and could have a substantial impact on these costs.

This study has several strengths. To the best of our knowledge, it is the first year-long telemedicine intervention of adults with T1D treated with insulin pumps that demonstrated the maintenance of glycemic control by telemedicine compared to standard care; as well as safety, maintenance of quality of life and satisfaction with treatment.

The telemedicine approach appears to be an effective and cost savings approach to T1D management in adults. For suitable patients, time-consuming routine visits may be replaced by easily available digital medicine. However, this alternative approach must be acceptable by the patient, as some prefer a more direct relationship with the physician. The lack of ability to conduct a physical exam and to perceive body language via phone and digital contact are main disadvantages of telemedicine. In addition, insurance coverage and physician responsibility are issues that must be resolved.

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Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

Ethical approval The local ethics committee Assuta Hospital Ramat HaHayal Israel approved the study, in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent All participant provided written consent.

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