Research Paper

Use of an integrated strip-free blood glucose monitoring system increases frequency of self-monitoring and improves glycemic control: Results from the ExAct study☆

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ABSTRACT

Aims: We investigated the impact of using an integrated, strip-free system compared to the use of single-strip systems on testing frequency and glycemic control in individuals with insulin-treated diabetes.
Methods: This multinational, comparative, cluster-randomized, observational study included 311 patients with type 1 and insulin-treated type 2 diabetes who were performing SMBG at suboptimal frequencies. Sites were cluster-randomized to "integrated strip-free" system (EXP group) or any "single-strip" system (CNL group). Testing frequency and HbA1c were measured at baseline, 12 weeks and 24 weeks.
Results: At week 24, the EXP group showed an increase in SMBG frequency from baseline of 4.17 tests/week (95% CI 2.76, 5.58) compared with an increase of 0.53 tests/week (95% CI −0.73, 1.79) among CNL patients, resulting in a between-group difference of 3.63 tests/week ($p < 0.0002$). Mixed-effects models for repeated measurements (MMRM) controlling for baseline frequency of testing, country and clinical site confirmed a higher SMBG testing frequency in the EXP group compared to the CNL group, with a between-group difference of 2.70 tests/week ($p < 0.01$). Univariate analysis showed greater HbA1c reductions in the EXP group than CNL group: −0.44% (95% CI −0.59, −0.29) vs. −0.13% (95% CI −0.27, 0.01), respectively, $p < 0.0002$. MMRM analyses confirmed these HbA1c reductions. A greater percentage of EXP than CNL patients achieved HbA1c reductions of ≥0.5%: 45.1% vs. 29.1%, respectively, $p < 0.01$.
Conclusions: The use of an integrated, strip-free SMBG system improved testing adherence and was associated with improvements in glycemic control.

Introduction

Self-monitoring of blood glucose (SMBG) is considered a critical component of effective management in individuals with type 1 diabetes and insulin-treated type 2 diabetes [1,2]. Appropriate use of SMBG can enhance self-management and support health care providers in determining individualized recommendations regarding lifestyle and medication [3], and it has been demonstrated to improve glycemic control in individuals with insulin-treated diabetes [4–6]. Recent studies have also shown that SMBG is beneficial in individuals with non-insulin-treated type 2 diabetes when a structured approach to testing is adopted [3,7–11].

National and international guidelines recommend frequent (≥3 daily) SMBG in individuals with type 1 and type 2 diabetes who are treated with multiple daily insulin injection (MDI) therapy, advising these individuals to perform SMBG prior to administering insulin in order to calculate appropriate basal and prandial insulin dosages (with occasionally postprandial tests), at bedtime, prior to exercise, and when symptoms of hypoglycemia are experienced [1,12,13]. Despite these recommendations, a large proportion of insulin-treated diabetes patients do not perform SMBG at optimal frequencies [14,15]. Although the cost of SMBG is often cited as a key obstacle to optimal testing frequency, inconvenience and interference with lifestyle may be a more significant factor in SMBG adherence. In a study of 62 insulin-treated diabetes patients by Nyomba and colleagues, 47% of participants reported inconvenience of testing as the primary reason for not performing frequent SMBG [16].

One recent advance in SMBG that may lessen the inconvenience of testing and, potentially, lead to greater adherence to recommended SMBG regimens is the development of integrated, strip-free systems such as the Accu-Chek Mobile System (Roche Diagnostics GmbH, Mannheim, Germany). The Experience in Accu-Chek Integrated Strip-free Systems (ExAct) study investigated the impact of using an integrated strip-free SMBG system compared to single-strip systems in a cohort of patients with type 1 and insulin-treated type 2 diabetes using self-adjusted insulin regimens.

Materials and methods

This 24-week, prospective, controlled, stratified, cluster-randomized, observational, international, multicenter study assessed changes in SMBG frequency and glycemic control in type 1 and insulin-treated type 2 diabetes patients, using the Accu-Chek Mobile system (experimental [EXP] group) compared with similar patients who were using any unspecified single-strip SMBG system (control [CNL] group). Investigators functioned independently in managing their patients. This study was conducted in accordance with the Declaration of Helsinki [17] and the guidelines of the International Organization for Standardization (ISO) 14155 were followed as applicable for a post-marketing study [18]. Informed consent was obtained from each patient prior to conducting any study-related procedures.

Randomization

Sixty study sites in Germany, the UK, Italy and the Netherlands were recruited for the study. Study inclusion required that sites must have qualified personnel and be equipped with the appropriate medical facilities to fulfill the study requirements. Additionally, the sites were required to be associated with and under the guidance of an independent ethics committee (IEC) to satisfy all regulatory authority requirements and to conduct meetings on a regular basis. Study sites were country-stratified and cluster-randomized (1:1) to the integrated strip-free system (Accu-Chek® Mobile System) or any single-strip system study arms but not matched for demographic characteristics. Envelopes with alternating group allocation were sent out by sequence of inclusion.

Patients

Patients were identified based on the usual care provided at the center they routinely attended and the investigator's assessment of the individual patient's clinical need. Selected patients were invited for screening and enrollment at baseline (week 0, Visit 0). Inclusion criteria for study participation were: ≥18 years of age; ≥1 year duration of diagnosed diabetes; initial HbA1c value of ≥7.0%, treatment with prandial insulin (regular insulin or rapid-acting insulin analog); self-adjustment of insulin dosages at each meal; and ≥12 weeks duration of SMBG at an average frequency <3.25 tests per day, using a current blood glucose meter with a minimum data capacity of 200 blood glucose measurements. Exclusion criteria included: use of parenterally administered drugs including, or being metabolized to, maltose, or oral or inhaled steroids; diagnosed with galactosemia or D-xylose malabsorption; pregnant or breastfeeding; current or planned chemotherapy or radiotherapy; current addiction to alcohol or other substances of abuse; or diagnosed with psychological conditions rendering the patient unable to understand the nature and scope of the study.

Procedures

At the screening visit (week 0), investigators established eligibility and identified patients who might not be able to follow the recommended SMBG regimen by checking the prescribing policy of the relevant general practitioner or diabetologist. After obtaining signed written informed consent from each patient, investigators performed physical assessments, documented medical histories and demographic information, obtained blood samples for HbA1c measurements and administered questionnaires to obtain patient-reported outcomes (PRO) data. Investigators uploaded data from each patient's current SMBG system memories. EXP patients were trained in the use of the integrated strip-free blood glucose monitoring system.

At follow-up visits, which occurred at weeks 12 and 24, investigators uploaded blood glucose meter data, obtained blood samples for HbA1c measurement, documented any adverse events and/or changes in patients' medications and administered PRO measures.

Blood glucose meters

Integrated strip-free SMBG-system

EXP patients used an integrated strip-free SMBG-system (Accu-Chek Mobile system), consisting of a device that contains a replaceable cassette that incorporates 50 tests on a continuous tape, so that SMBG can be performed on the device. The device was designed to lessen test complexity and reduce the number of handling steps, which can affect patients' adherence to recommended testing frequencies [19,20]. The system also utilizes new lancing device technology, enabling nearly pain-free testing, which can impact patient adherence [21].

Single-strip SMBG-systems

CNL patients used any standard, currently marketed single-strip SMBG-system from any manufacturer. It was required that the device was capable of data capture with a minimum capacity of 200 blood glucose measurements over a period of 4 weeks and allow electronic upload of these data.

Provision of blood glucose meters/testing supplies

Patients in both study groups were responsible for obtaining reimbursement for their blood glucose testing supplies from their

current healthcare insurers, which eliminated any potential for participants or physicians to feel any gratitude toward the sponsor. Because access to testing supplies varies by country, sites were stratified within each country prior to randomization to achieve equal access to testing supplies in both groups.

Measurements

The primary study endpoint was the change from baseline in the mean test frequency at week 24. SMBG frequency at baseline and follow-up visits was assessed using patients' respective SMBG system memories. Secondary endpoints assessed changes in HbA1c (e.g., between-group differences at week 24, proportion of patients who achieved ≥0.5% HbA1c reduction [high achievers] from baseline). HbA1c was assessed at baseline and weeks 12 and 24. Validated instruments were used to assess PRO measures, including the: SMBG survey to assess patients' attitudes regarding blood glucose monitoring [22]; the EQ-5D health status measure [23]; Diabetes Treatment Satisfaction Questionnaire (DTSQ) to assess patients' satisfaction with their treatment regimens [24,25]; and regimen-related distress subscale from the Diabetes Distress Scale (DDS) to assess patients' emotional distress related to their treatment regimen [26]. The investigator-developed Treatment Adherence and Barriers (TAB) measure was used to assess patients' reasons for adherence and nonadherence. All of the PRO measures were assessed using self-administered questionnaires.

Statistical analysis

The analysis population was defined as all eligible patients who provided signed informed consent, participated in the baseline visit and for whom at least one post-baseline observation on the primary endpoint was available. Sample size estimation was based on the results of a previous user survey [5]; it was assumed that the change in test frequency from baseline in patients using the integrated strip-free SMBG system and patients using single-strip SMBG systems would differ by 3 tests per week relative to a within-group standard deviation of 11 tests per week. The sample size of 478 enrolled patients combined with an observed average number of 6.4 patients per center and an assumed intra-cluster correlation of <0.01 was considered sufficient to provide at least 80% power for this study. The primary analysis addressed the difference in changes in test frequency between the two device groups, which was assessed by means of a two-sided t-test at a significance level of 5%. The last observation was carried forward if ≥1 post-baseline value was available to impute missing values. Mixed-effects models for repeated measurements (MMRM) were also used to analyze the change in average test frequency and in HbA1c from baseline to both follow-up visits as dependent variables [27,28]. These model-based analyses support the evidence of the primary analyses and were performed to address the following objectives to evaluate and adjust for effects of co-factors (e.g., differences in dependent variables among countries), adjust for differences in covariates such as the baseline test frequency, allow for missing data under the missing-at-random assumption [29] and account for a possible intra-cluster correlation [27]. The analysis of HbA1c also included test frequency at each visit as a time-dependent covariate. Sites with <4 patients per country and device group were pooled for analyses to account for center effect. Within-patient variation was modeled as a random effect, with unstructured covariance matrix and center as random factor; the latter to account for a possible cluster effect [27].

High achiever rates were analyzed based on the number and percentage of patients who achieved >0.5% HbA1c reduction from baseline at week 24 by device group, using Fisher's exact test. Selected demographic and baseline variables across device group were compared using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Results

Subject disposition and demographics

The study was conducted from October 2010 to July 2012 at centers in Germany, the UK, Italy, and the Netherlands. Sixty study centers were stratified by country and then randomized to account for country differences in blood glucose test strip reimbursement. A total of 55 centers (29 EXP, 26 CNL) enrolled patients and completed the study; five centers withdrew from the study immediately following site randomization. A total of 478 patients from 55 centers (Germany: 28 centers, $n = 222$ [46.44%]; Italy: 10 centers, $n = 119$ [24.89%]; United Kingdom: 9 centers, $n = 75$ [15.69%]; the Netherlands: 8 centers, $n = 62$ [12.97%]) were screened for eligibility for study participation. Of 478 patients screened, 405 met study inclusion criteria, 22 were excluded because they failed an inclusion criteria checklist, 29 were excluded because they used an impermissible meter at baseline, and 22 had SMBG testing frequencies at baseline that exceeded study inclusion criteria. Of those eligible, 350 patients began the study, and 311 patients had post-baseline observations on the study primary endpoint: 144 (46.30%) in the EXP group and 167 (53.70%) in the CNL group). This group comprised the efficacy analysis sample; data analysis was based on this population (Figure 1).

Among the population analyzed ($n = 311$), most patients were male ($n = 191$; 61.41%), Caucasian ($n = 298$; 95.82%) and aged ≥65 years ($n = 214$; 68.8%). The proportion of patients with type 1 and insulin-treated type 2 diabetes was 28.9% and 71.06%, respectively. At baseline, some patient characteristics differed by device group (Table 1). Most notably, EXP patients had significantly lower mean weekly SMBG testing frequency (11.03 vs. 12.73, $p < 0.05$) and marginally higher HbA1c (8.60% vs. 8.37%, $p < 0.09$). These discrepancies were corrected for during statistical analysis of the results, as described in the Methods section.

Changes in SMBG frequency

At week 24, EXP patients showed an average increase in SMBG frequency of 4.17 (95% CI 2.76, 5.58) tests per week (Δ 0.60 tests per day) while CNL patients showed an increase of 0.53 (95% CI −0.73, 1.79) tests per week (Δ 0.08 tests per day), resulting in a between-group difference in the average weekly SMBG testing frequency of 3.63 tests/week ($p < 0.0002$) (Figure 2A). MMRM analyses (adjusted data) also showed a greater increase in testing frequency from baseline at week 24 in EXP patients (3.46 [95% CI 1.96, 4.97]) than CNL patients (0.76 [95% CI −0.65, 2.18]), resulting in a between group difference of 2.70 tests/week ($p < 0.01$). The differences in change in test frequency were also evident at week 12 in both univariate and MMRM analyses.

Changes in HbA1c values

At week 24, univariate analysis showed a greater decrease in HbA1c from baseline in EXP patients than CNL patients: −0.44% (95% CI −0.59, −0.29) vs. −0.13% (−0.27, 0.01), $p < 0.0002$ (Figure 2B). The decreases in mean HbA1c values were greater at week 12 for EXP patients compared with CNL patients: −0.45% (95% CI −0.59, −0.31) vs. −0.20% (95% CI −0.33, −0.07), respectively, $p < 0.02$. Although the mean change in HbA1c from week 12 to week 24 was maintained in EXP patients, CNL patients showed slight increases in HbA1c levels between week 12 and week 24. Similar findings were seen MMRM analysis.
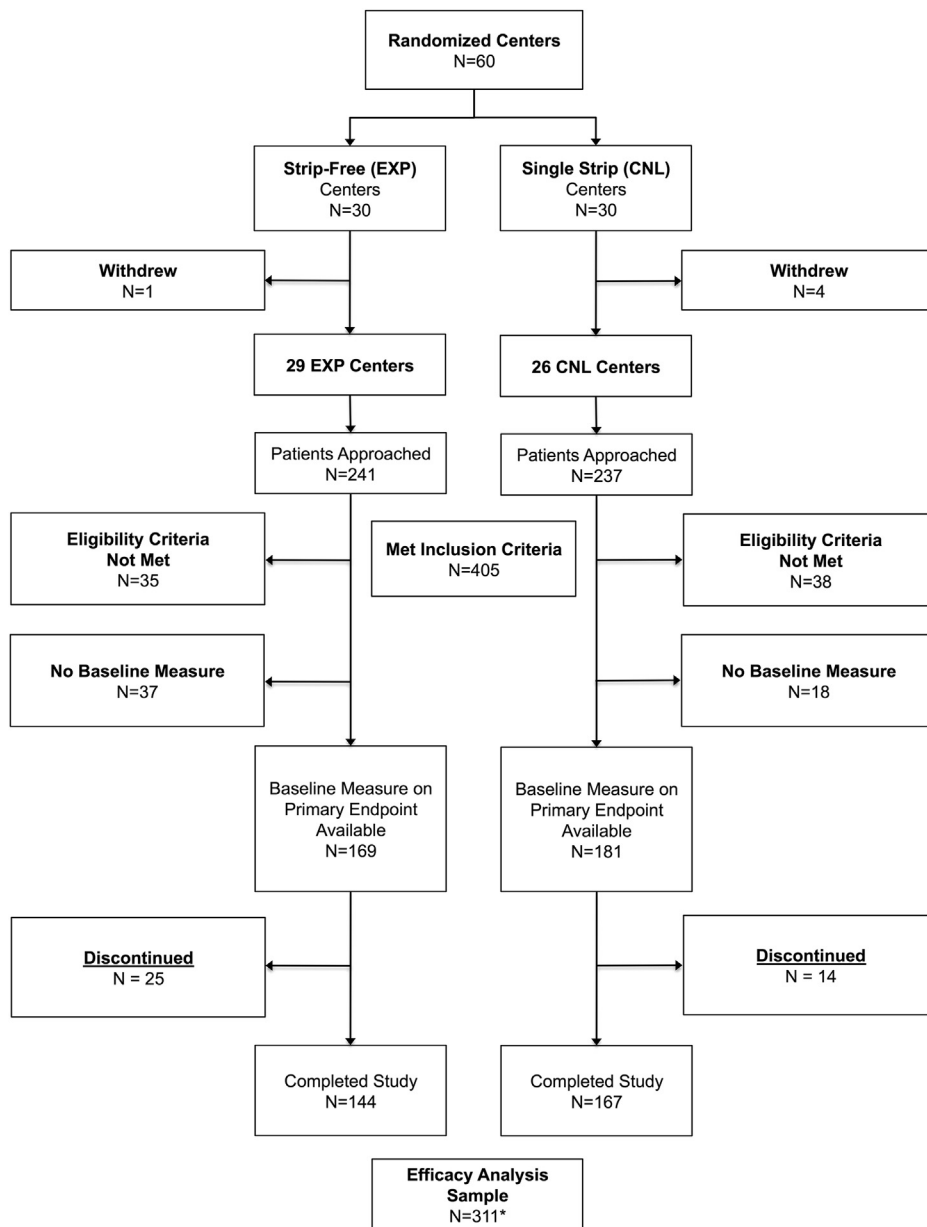
Figure 1. Subject disposition.

A greater percentage of EXP than CNL patients achieved HbA1c reductions of ≥0.5% at week 24: 45.14% vs. 29.09%, respectively, $p < 0.01$). Reductions in mean (SD) HbA1c at week 24 among high achievers were similar between EXP and CNL patients: −1.03 (0.69)% vs. −0.91 (0.65)%, $p = $ NS.

Changes in psychosocial measures

Analyses of aggregated PRO variables revealed no changes over time or device group differences on any of the patient-reported outcomes assessed in this study, which included measures of diabetes treatment satisfaction, diabetes-related distress or treatment. However, sub-score analyses showed a non-significant tendency for slightly more positive perceived change in the frequency of hyperglycemia and hypoglycemia for patients in the EXP group than in the CNL group. Additional analyses of these measures and others will be presented in a subsequent report.

Safety

The number of patients with diabetes-related events was extremely low and similar for both device groups. One patient randomized to the single-strip device group reported a diabetes-related event that led to hospitalization. No patients died during the study and no patients discontinued the study due to diabetes-related events.

Discussion

This study compared the impact of a strip-free SMBG system with a single-strip system on patient adherence to SMBG measurement frequency and glycemic control. At the start of the study, patients in both groups were performing SMBG at less than the recommended frequency of ≥3 tests per day [1,12,13], which is generally required for accurate calculation and effective adjustment of insulin dosages.

Table 1
Baseline characteristics of eligible patients

Characteristic	Integrated strip-free system N = 144	Single-strip system N = 167	p-Value[a]
Age, mean years (SD)	55.04 (16.28)	58.75 (14.35)	0.035
BMI, mean kg/m^2 (SD)	30.77 (6.35)	31.52 (6.51)	0.308
Test frequency per week, mean (SD)	11.03 (6.70)	12.73 (6.99)	0.030
HbA1c, mean % (SD)	8.60 (1.17)	8.37 (1.16)	0.089
Diabetes duration, mean years (SD)	15.58 (9.02)	16.82 (10.04)	0.263

[a] *p*-Value results from two-sided Wilcoxon rank sum test. BMI = body mass index; HbA1c = glycosylated hemoglobin; SD = standard deviation.

After 12 weeks, use of an integrated strip-free SMBG system resulted in a significantly greater increases in mean SMBG testing frequency compared with single-strip systems. At week 24, the mean SMBG frequency in the strip-free system group remained significantly greater than baseline, while testing frequency in the single-strip system decreased to baseline levels. Although we failed to recruit and retain all patients who were approached for this study (N = 478), the observed study power for the tests of treatment differences were not adversely affected because the observed change in SMBG frequency was significantly greater (with lower standard deviation) than anticipated.

There was a significant association between change in HbA1c from baseline and use of the strip-free system. As reported, the increased SMBG frequency in the EXP group was accompanied by significant reductions in HbA1c values from baseline after 12 weeks, which were maintained through week 24. The improvement

EXP vs. CNL at 12 weeks, P<0.01; EXP vs. CNL at 12 weeks (adjusted), P<0.2

EXP vs. CNL at 12 weeks, P<0.02; EXP vs. CNL at 12 weeks (adjusted), P<0.04

Figure 2. Change over time in (A) mean weekly SMBG frequency and (B) mean HbA1c values.

in glycemic control in the strip-free system group compared with the single-strip system group also remained significant after multivariate analysis that included HbA1c level at baseline. Moreover, a greater proportion of patients in the EXP group achieved a clinically relevant decrease of ≥0.5% in HbA1c from baseline to week 24 compared with the CNL group.

The glycemic improvements seen in our study may be due to more accurate and/or frequent bolus insulin dosage calculations. Because manual calculation of bolus insulin dosages is complex and time consuming, patients often do not perform these calculations and, instead, rely on empirical estimates, which can lead to poor glycemic control (hypoglycemia and hyperglycemia) [30]. Although patients were provided no additional tools to aid in their bolus calculations, it is possible that changes in their behavior regarding SMBG frequency may have influenced their willingness to appropriately and more frequently calculate their prandial insulin dosages.

A key limitation of the study was a probable selection bias among clinicians. As described earlier, investigating clinicians selected patients based on their assessment of each patient's clinical need. If EXP clinicians did, indeed, select less adherent and/or less well-controlled patients, this would likely explain the imbalances seen in baseline HbA1c levels and SMBG frequency. However, it would also suggest that EXP clinicians recognized the potential value and utility of the strip-free system relevant to these patients and that the strip-free system achieved significant gains in testing frequency and HbA1c reduction with potentially more adherence-challenged patients. Although additional multivariate analyses methodologies were performed to control for these baseline differences, we recognize the potential of these imbalances to influence our findings. A more traditional randomization scheme would have limited selection bias by minimizing clinician discretion at study initiation; however, we chose a cluster-randomized study design to avoid any potential "cross-contamination" of study participants, both patients and clinicians, which can occur throughout the course of an unblinded study when "within-clinic" randomization is utilized [2].

Another possible limitation of the study was the potential influence of the "novelty effect" among EXP patients. We recognize that receiving a new blood glucose meter would likely prompt increased SMBG frequency among patients during the first few weeks of the study, and that this increased frequency would then subside over time. This was not observed in our study; the increased SMBG frequency and associated improvements in HbA1c that occurred between weeks 0 and 12 within the EXP group were sustained for the duration of the study, suggesting that the increased SMBG frequency may have provided a greater amount of meaningful information that facilitated patients' ability to make more appropriate therapeutic decisions. Moreover, one might have expected CNL patients to maintain their current monitoring frequency, and even increase their frequency due to the study effect [31]. Monitoring frequency in CNL patients showed a modest increase during the first 12 weeks of the study (significantly less than that achieved by EXP patients at week 12) and then declined to baseline levels at the end of the study. Although modest HbA1c improvements were seen in the CNL group at weeks 12, albeit, significantly less than that achieved by EXP patients, CNL group glycemic control deteriorated from week 12 to week 24 in direct proportion to decreased SMBG frequency. Lack of standardization of meters used by CNL patients is also a possible limitation due to differences in meter testing procedures and ease of use.

In conclusion, this is the first study to explore the potential impact of an integrated strip-free SMBG system on SMBG frequency and glycemic control in a large, international patient population. Results from the ExAct study demonstrated that the use of the Accu-Chek® Mobile System can lead to significant increases in the frequency of SMBG tests towards guideline-recommended values in
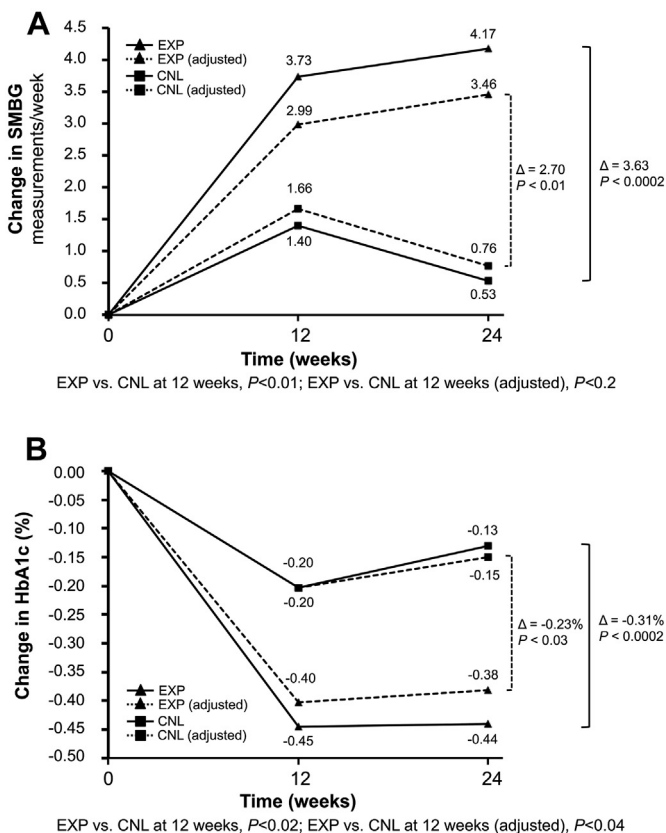
previously non-adherent patients and to improvements in glycemic control. Importantly, the SMBG and glycemic improvements seen with the integrated strip-free technology were maintained throughout the study period, suggesting that patients had better awareness of their glucose levels and were able to make the necessary adjustments to their medication and diet in a timely manner, thus supporting adherence to their medication. Although additional studies are needed to further stratify the changes in SMBG testing frequency to type 1 or type 2 diabetes patients in order to determine whether one type of patient is more responsive to the new technology than the other, our findings suggest that the benefits of an integrated strip-free SMBG system may be generalizable across a large range of individuals with insulin-treated diabetes.

Acknowledgments

References

[1] Standards of medical care in diabetes – 2013. Diabetes Care 2013;36(Suppl. 1): S11–66.

[2] Global guideline on self-monitoring of blood glucose in non-insulin treated type 2 diabetes. International Diabetes Federation; 2009. Available from: http://www.idf.org/webdata/docs/SMBG_EN2.pdf. Accessed 03.11.13.

[3] Parkin CG, Buskirk A, Hinnen DA, Axel-Schweitzer M. Results that matter: structured vs. unstructured self-monitoring of blood glucose in type 2 diabetes. Diabetes Res Clin Pract 2012;97:6–15.

[4] Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.

[5] Schutt M, Kern W, Krause U, Busch P, Dapp A, Grziwotz R, et al. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Exp Clin Endocrinol Diabetes 2006;114:384–8.

[6] Lalic N, Tankova T, Nourredine M, Parkin C, Schweppe U, Amann-Zalan I. Value and utility of structured self-monitoring of blood glucose in real world clinical practice: findings from a multinational observational study. Diabetes Technol Ther 2012;14:338–43.

[7] Polonsky WH, Fisher L, Schikman C, Hinnen DA, Parkin CG, Jelsovsky Z, et al. A structured self-monitoring of blood glucose approach in type 2 diabetes encourages more frequent, intensive, and effective physician interventions: results from the STeP study. Diabetes Technol Ther 2011;13(8):797–802.

[8] Polonsky WH, Fisher L, Schikman CH, Hinnen DA, Parkin CG, Jelsovsky Z, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the structured testing program study. Diabetes Care 2011;34:262–7.

[9] Kempf K, Kruse J, Martin S. Rosso-in-praxi: a self-monitoring of blood glucose-structured 12-week lifestyle intervention significantly improves glucometabolic control of patients with type 2 diabetes mellitus. Diabetes Technol Ther 2010;12:547–53.

[10] Kempf K, Kruse J, Martin S. Rosso-in-Praxi follow-up: long-term effects of self-monitoring of blood glucose on weight, hemoglobin a1c, and quality of life in patients with type 2 diabetes mellitus. Diabetes Technol Ther 2012;14(1): 59–64.

[11] Schnell O, Amann-Zalan I, Jelsovsky Z, Moritz A, Bermejo JL, Parkin CG, et al. Changes in A1C levels are significantly associated with changes in levels of the cardiovascular risk biomarker hs-CRP: results from the STeP study. Diabetes Care 2013;36:2084–9.

[12] Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011;17(Suppl. 2):1–53.

[13] Global IDF/ISPAD guideline for diabetes in childhood and adolescence. International Diabetes Federation; 2011. Available from: http://www.Idf.Org/sites/default/files/diabetes-in-childhood-and-adolescence-guidelines.pdf. Accessed 03.11.13.

[14] Moreland EC, Volkening LK, Lawlor MT, Chalmers KA, Anderson BJ, Laffel LM. Use of a blood glucose monitoring manual to enhance monitoring adherence in adults with diabetes: a randomized controlled trial. Arch Intern Med 2006;166:689–95.

[15] Brindisi MC, Hahn J, Chiasson JL, Rabasa-Lhoret R. Under-utilization of capillary glucose monitoring by type 2 diabetic patients. Diabetes Res Clin Pract 2007;75:123–5.

[16] Nyomba BL, Berard L, Murphy LJ. The cost of self-monitoring of blood glucose is an important factor limiting glycemic control in diabetic patients. Diabetes Care 2002;25:1244–5.

[17] World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. J Am Med Assoc 1997;277:925–6.

[18] International Organization for Standardization (ISO). ISO 14155:2011: clinical investigation of medical devices for human subjects – good clinical practice. Available from: http://www.Iso.Org/iso/catalogue_detail?Csnumber=45557; Accessed 12.11.13.

[19] Bergenstal R, Pearson J, Cembrowski GS, Bina D, Davidson J, List S. Identifying variables associated with inaccurate self-monitoring of blood glucose: proposed guidelines to improve accuracy. Diabetes Educ 2000;26:981–9.

[20] Wijsman I. Patient-reported barriers in diabetes management and areas of opportunity for healthcare professionals (abstract). FEND 14th Annual Conference, Vienna, 2009.

[21] Le Floch JP, Bauduceau B, Levy M, Mosnier-Pudar H, Sachon C, Kakou B. Self-monitoring of blood glucose, cutaneous finger injury, and sensory loss in diabetic patients. Diabetes Care 2008;31:e73.

[22] Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. Diabetes Care 2000;23:943–50.

[23] Kind P. The EUROQOL instrument: an index of health-related quality of life. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. Lippincott-Raven; 1995.

[24] Bradley C. The diabetes treatment satisfaction Questionnaire: DTSQ. In: Bradley D, editor. Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice. Chur, Switzerland: Harwood Academic Publishers; 1994. p. 111–32.

[25] Bradley C. Diabetes Treatment Satisfaction Questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. Diabetes Care 1999;22:530–2.

[26] Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, et al. Assessing psychosocial distress in diabetes: development of the Diabetes Distress Scale. Diabetes Care 2005;28:626–31.

[27] Donner A, Klar N. The role of cluster randomization trials in health research. New York: Oxford University Press; 2000.

[28] Brown H, Prescott R. Applied mixed models in medicine. 2nd ed. John Wiley & Sons; 2006.

[29] Siddiqui O. MMRM versus mi in dealing with missing data – a comparison based on 25 NDA data sets. J Biopharm Stat 2011;21:423–36.

[30] Gross TM, Kayne D, King A, Rother C, Juth S. A bolus calculator is an effective means of controlling postprandial glycemia in patients on insulin pump therapy. Diabetes Technol Ther 2003;5:365–9.

[31] De Amici D, Klersy C, Ramajoli F, Brustia L, Politi P. Impact of the Hawthorne effect in a longitudinal clinical study: the case of anesthesia. Control Clin Trials 2000;21:103–14.