The Diabeo Software Enabling Individualized Insulin Dose Adjustments Combined With Telemedicine Support Improves HbA$_1c$ in Poorly Controlled Type 1 Diabetic Patients

A six-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study)

Guillaume Charpentier, MD$^1$
Pierre-Yves Benhamou, MD, PhD$^2$
Dured Dardari, MD$^3$
Annie Clerget, MD$^1$
Sylvia Franc, MD$^1$
Pauline Schaepelynck-Belicar, MD$^4$
Bogdan Catargi, MD, PhD$^5$

Vincent Melki, MD$^6$
Lucy Charlous, MD$^7$
Anne Farret, MD$^8$
Jean-Luc Bosson, MD, PhD$^9$
Alfred Penfornis, MD, PhD$^3$

ON BEHALF OF THE TELEDIAB STUDY GROUP*

OBJECTIVE—To demonstrate that Diabeo software enabling individualized insulin dose adjustments combined with telemedicine support significantly improves HbA$_1c$ in poorly controlled type 1 diabetic patients.

RESEARCH DESIGN AND METHODS—In a six-month open-label parallel-group, multicenter study, adult patients ($n=180$) with type 1 diabetes ($\geq$1 year), on a basal-bolus insulin regimen ($\geq$6 months), with HbA$_1c$ $\geq$8%, were randomized to usual quarterly follow-up (G1), home use of a smartphone recommending insulin doses with quarterly visits (G2), or use of the smartphone with short teleconsultations every two weeks but no visit until point end (G3).

RESULTS—Six-month mean HbA$_1c$ in G3 ($8.41 \pm 1.04\%$) was lower than in G1 ($9.10 \pm 1.16\%$; $P = 0.0019$). G2 displayed intermediate results ($8.63 \pm 1.07\%$). The Diabeo system gave a 0.91% (0.60; 1.21) improvement in HbA$_1c$ over controls and a 0.67% (0.35; 0.99) reduction when used without teleconsultation. There was no difference in the frequency of hypoglycemic episodes or in medical time spent for hospital or telephone consultations. However, patients in G1 and G2 spent nearly 5 h more than G3 patients attending hospital visits.

CONCLUSIONS—The Diabeo system gives a substantial improvement to metabolic control in chronic, poorly controlled type 1 diabetic patients without requiring more medical time and at a lower overall cost for the patient than usual care.

HbA$_1c$ remains unsatisfactory in many patients of type 1 diabetes with levels consistently above 8.0%, despite close monitoring and participation in educational programs, with the American Diabetes Association recommended therapy for type 1 diabetes (basal and prandial analog insulin, either with multiple daily injections [MDI] or insulin pump) (1–3). Prandial insulin has to be adjusted according to carbohydrate intake, premeal blood glucose, and anticipated physical activity (4). The main reasons for these unsatisfactory results are: patient difficulty in coping with the constraints of the disease; difficulty applying the complex determination of the required amount of prandial insulin, leading to incorrect insulin doses and thus to hypo- or, more often, hyperglycemia; finally, patients may find it difficult to comply with scheduled doctor visits since they need to take a day off for their medical visit. Another difficulty arises from the patient’s paper diary, currently the usual tool of data communication between patients and diabetologists. It is often perceived as a boring document and therefore may be poorly filled in. In such cases, the diabetologist has limited information to recommend the appropriate insulin dose. The blood glucose measurements stored in the memory of the patient’s meter are of little use without reliable information on the time and content of meals, physical activity, or insulin doses injected.

We have created the Diabeo system to overcome some of these hurdles. Diabeo is a software uploaded onto smartphones with internet connection that provides to the patient 1 bolus calculators using validated algorithms, taking into account carbohydrate intake, premeal blood glucose,
Diabeo software improves type 1 diabetes HbA1c

and anticipated physical activity reported by the patient; 2) plasma glucose targets; 3) automatic algorithms for the adjustment of carbohydrate ratio and basal insulin or pump basal rates when the postprandial or fasting plasma glucose levels are off target; 4) data transmission to medical staff computers, through General Packet Radio Service (GPRS) and secured websites, to allow easy telemonitoring and teleconsultations. One pilot single-center study has demonstrated the feasibility, safety and accuracy of Diabeo (5). The aim of this study was to evaluate the efficiency of the Diabeo system in improving metabolic control of chronic, poorly controlled type 1 diabetes.

RESEARCH DESIGN AND METHODS—Participants were over 18 years old, had type 1 diabetes for at least 1 year, and had been treated with a basal bolus insulin regimen for at least 6 months, either with MDI or with a pump. They were eligible for the study if their last HbA1c values during the year before and at entry of the study were ≥8.0%. Participants were asked to carry out at least two self-monitoring plasma glucose (SMPG) everyday during the study. Exclusion criteria were participation in a diabetes educational program within 3 months before the study or a clinical condition requiring the patient to receive follow-up more frequently than the quarterly visits scheduled. All participants provided written consent before any study procedures were started. The protocol, consent forms, and patient information sheets were approved by the ethics committee of medical university Paris VI.

Trial design and interventions
This study was a 6-month randomized, open-label, parallel-group trial, involving 17 hospital sites in France. Participants were randomly assigned to three groups of equal size. Participants in the control group (G1) had no electronic logbook but kept their paper logbook and were asked to attend two follow-up visits at the hospital, after 3 and 6 months. Participants randomized to group G2 received a smartphone loaded with the Diabeo software. They did not use the teleconsultation option, but face-to-face follow-up visits were planned for month 3 and month 6. Participants randomized to group G3 received a smartphone with the Diabeo software. No follow-up hospital visits were scheduled, until end point at month 6, but teleconsultations by telephone call were planned every 2 weeks. Participant SMPG, diet, and insulin treatment data were automatically uploaded by the smartphone to a secured website, where they were available to investigators at any time, including during the teleconsultations. Teleconsultations were conducted with both patients and doctors in front of their computers or smartphone displaying last weeks' data and focused on insulin dose adjustments and motivational support. Randomization was carried out using a Web-based system. Data were collected in an electronic case-report form (Clininfo, Lyon, France). The study began in September 2007 and ended in April 2009.

Diabeo software is a bolus calculator with validated algorithms (5), taking into account SMPG level before meals, carbohydrate counts, and planned physical activity. Parameters personally tailored for adjustment of prandial and basal insulin dose are entered into the system for each patient. If fasting or postprandial SMPG do not meet target levels, the system can suggest adjustments for carbohydrate ratio, long-acting insulin analog dose, or pump basal rates. Diabeo software was edited by Voluntis (Paris, France), in collaboration with CERITD.

The primary efficacy outcome was HbA1c levels at end point. HbA1c high-performance liquid chromatography (HPLC) assays were performed at baseline and end point on the hospital site. Secondary efficacy end points included the change in the HbA1c level from baseline to end point, the proportion of patients reaching the HbA1c target of below 7.5%, the change in SMPG frequency, the change in quality of life (QOL) and satisfaction assessed by Diabetes Health Profile and Diabetes QOL questionnaires, the amount of time spent by investigators conducting face-to-face visits or teleconsultations, and by the participants coming for hospital visits (6,7). For G2 and G3 participants, satisfaction with Diabeo system and their willingness to carry on with it at the end of the study was assessed by a specific questionnaire.

Safety variables included major hypoglycemia episodes, defined as requiring third-party assistance, and minor hypoglycemia episodes, defined as symptomatic, nonsevere hypoglycemia self-reported by the participant within 14 days before baseline and end point visits.

Statistical analysis
To detect a 0.7% difference in HbA1c at month 6 (with a baseline mean ± SD of 9.0 ± 1.2%), 48 subjects were needed in each group to give 80% power with a two-sided test. To maintain the risk of error at 0.05, we used a significance level for P = 0.017 (Bonferroni adjustment for multiple comparisons on the primary end point). 180 subjects were enrolled and randomized into three groups. Efficacy outcomes were analyzed on an intention-to-treat basis. Categorical data were expressed as frequencies and percentages; quantitative data were expressed as means and standard deviation. Kruskal-Wallis and Mann-Whitney tests with α-adjustment were used assuming a non-Gaussian distribution. The primary end point, HbA1c at month 6, was analyzed with Kruskal-Wallis and Mann-Whitney tests with α-adjustment (α/3) for group comparisons. The ANCOVA analysis was used to confirm the results on the primary end point, HbA1c level at 6 months, taking into account age and HbA1c at baseline as covariates. Missing data were imputed with the last observation carried forward. It was decided from the outset that for such patients, missing values could be replaced by HbA1c measurements taken at month 6 in a private laboratory, provided the upper normal range limit was ≤6.0%. If no result was available at month 6, HbA1c measured at month 3 was used. Secondary quantitative outcomes were analyzed similarly. The number of patients who need to be treated, and the effect size with CI95%, was calculated. Cohen d effect size is defined as the difference between two means (month 0 and month 6) divided by the pooled standard deviation for the data.

All analyses were performed using Stata 10.1 (StataCorp, College Station, TX).

RESULTS—We randomly assigned 180 participants to groups G1 (n = 61), G2 (n = 60), and G3 (n = 59). For 162 patients, a HbA1c hospital measurement was available for end point analysis; for the remaining 11 patients, a surrogate was used: missing values were replaced either by HbA1c measurements taken at month 6 in a private laboratory, provided the upper normal range limit was ≤6.0% (n = 6). If no result was available at month 6, HbA1c measures at month 3 were used (n = 5). Seven participants were lost to follow-up and/or had missing HbA1c data at month 6 (Fig. 1). Thus we
analyzed 173 participants for their main end point result at month 6.

Although the main inclusion criterion was HbA1c ≥8%, 10 participants were included with HbA1c below 8%. These participants were equally distributed between the three groups; their data were retained for analysis. The characteristics of the study population are shown in Table 1 and are well matched between groups.

Mean HbA1c was 9.07 ± 1.07% at baseline, similar to values determined 1 week (9.04 ± 0.80%) and 3 months (9.34 ± 1.34%) before. No difference was observed between groups. These values are consistent with poorly controlled chronic diabetes. End point HbA1c was higher in G1 (9.10 ± 1.16%) than in G2 (8.63 ± 1.07%, P = 0.022) and G3 (8.41 ± 1.04%, P = 0.0019). After an adjustment for multiple comparisons (α’ = 0.017), the difference between G1 and G2 end point values was no longer statistically significant; however, the difference between G1 and G3 remained significant. Previous results remained significant after an adjustment on age and HbA1c at baseline (Supplementary Table 1). Similar results were obtained when analyzing the 162 HbA1c hospital laboratory measurements that were available at end point, before replacement of the missing data. Improvement in HbA1c values was observed as early as month 3 (Fig. 2A). The difference in HbA1c reduction was highly significant (P < 0.001) between G1 and G2 (0.67% [0.35–0.99%]) or G3 (0.91% [0.60–1.21%]), but not between G2 and G3 (Fig. 2B and Supplementary Table 2). The effect size was low in G1 (0.17 [−0.19–0.53]), median in G2 (0.47 [0.09–0.84]), and large (0.66 [0.28–1.04]) in G3.

The proportion of participants reaching the target of HbA1c ≤7.5% at end point was 17% (n = 10) in G3, 6.7% (n = 4) in G2, and 1.6% (n = 1) in G1. The difference between G3 and G1 was highly significant (P = 0.007). The number of patients who need to be treated was seven for G3 and 20 for G2. The mean number of daily SMPG for the 14 days before month 0 was 3.29 ± 1.44 and did not differ significantly between groups. A slightly higher daily frequency of SMPG was observed for the 14 days before the end point visit (3.57 ± 1.35, P = 0.036), but with similar increases in the three groups and without difference in SMPG frequency between groups.

HbA1c level did not significantly differ in each group between MDI and continuous subcutaneous insulin infusion (CSII). There were no significant insulin dose modifications between groups (Supplementary Table 5).

The frequency of symptomatic, non-severe hypoglycemia episodes reported by participants for the 14 days before visits did not differ between groups at end point (4.6 ± 4.0) and did not increase from the baseline (3.7 ± 3.2). Three participants in G1 and G2, and one participant in G3, experienced severe episodes.
Diabeo software improves type 1 diabetes HbA1c

Table 1—Demographic and baseline characteristics. Data are means ± SD or numbers (%)

<table>
<thead>
<tr>
<th></th>
<th>Whole population</th>
<th>G1 control</th>
<th>G2 electronic logbook alone</th>
<th>G3 electronic logbook + teleconsultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (randomized)</td>
<td>180</td>
<td>61</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>N baseline HbA1c &lt;8%</td>
<td>10 (5.6%)</td>
<td>4 (6.6%)</td>
<td>2 (3.3%)</td>
<td>4 (6.8%)</td>
</tr>
<tr>
<td>Men</td>
<td>66 (36.7%)</td>
<td>21 (34.4%)</td>
<td>23 (38.3%)</td>
<td>22 (37.3%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.8 ± 12.9</td>
<td>36.8 ± 14.1</td>
<td>32.9 ± 11.7</td>
<td>31.6 ± 12.5</td>
</tr>
<tr>
<td>Highest level of school education completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low level (college or less)</td>
<td>42 (23.5%)</td>
<td>14 (23.0%)</td>
<td>13 (22.0%)</td>
<td>15 (25.4%)</td>
</tr>
<tr>
<td>Intermediate level (less than university degree)</td>
<td>38 (21.2%)</td>
<td>13 (21.3%)</td>
<td>12 (20.3%)</td>
<td>13 (22.0%)</td>
</tr>
<tr>
<td>High level (university degree)</td>
<td>99 (55.3%)</td>
<td>34 (55.7%)</td>
<td>34 (57.6%)</td>
<td>31 (52.5%)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.9 ± 5.2</td>
<td>25.1 ± 6.8</td>
<td>23.8 ± 3.3</td>
<td>25.8 ± 5</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>16.4 ± 9.6</td>
<td>16.9 ± 10.5</td>
<td>17.6 ± 8.9</td>
<td>14.7 ± 9.1</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>52/173 (30.1%)</td>
<td>17/58 (29.3%)</td>
<td>23/59 (39%)</td>
<td>12/56 (21.4%)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>21/177 (11.9%)</td>
<td>4/58 (6.9%)</td>
<td>10 (16.7%)</td>
<td>7 (11.9%)</td>
</tr>
<tr>
<td>Clinical neuropathy</td>
<td>20/178 (11.2%)</td>
<td>9/59 (15.3%)</td>
<td>4 (6.7%)</td>
<td>7 (11.9%)</td>
</tr>
<tr>
<td>Insulin pump</td>
<td>36.7% (66)</td>
<td>36.1% (22)</td>
<td>36.7% (22)</td>
<td>36.7% (22)</td>
</tr>
<tr>
<td>HbA1c at baseline</td>
<td>9.07 ± 1.07</td>
<td>8.91 ± 0.90</td>
<td>9.19 ± 1.14</td>
<td>9.11 ± 1.14</td>
</tr>
</tbody>
</table>

during the 6 months of the study. The frequency of these episodes did not differ from the one reported for the year preceding the study.

QOL at baseline and end point, determined by assessment of satisfaction in the DQOL and by DHP questionnaires, did not differ between groups (Supplementary Table 3 and Supplementary Table 4). At month 6, 67% of G2 participants and 75% of G3 participants stated that they wanted to continue with the system for routine follow-up, upon agreement with their doctor. The only difference between patients willing to continue with Diabeo was a better improvement in HbA1c at end point (8.39 ± 0.80 vs. 8.50 ± 0.10, P = 0.033) in those who wanted to carry on. Investigators (77%) said that they were satisfied or very satisfied with Diabeo.

To evaluate the time spent by doctors delivering care to patients, we recorded the duration of visits at month 3 and month 6 in G1 and G2 and the duration of teleconsultations in G3. The average duration of time spent during follow-up was 70 ± 31 min in G1 and 70 ± 22 min in G2, for the two visits, and 72 ± 30 min in G3, for teleconsultations (mean number of teleconsultations: 8.7 ± 4.9; mean duration for one teleconsultation: 7.4 ± 3 min). There was no difference between the three groups for the total time spent on follow-up, whether face to face or by telephone. However, for participants in G1 and G2, an additional 274 ± 178 min were spent by participants in G1 and 288 ± 218 min for G2 traveling to and from the hospital, carrying out administrative procedures, and waiting time, whereas G3 participants did lose overtime. Significantly, the software did not require more time for the patient to manage diabetes. The main additional time combined the launching of the software on the smartphone, the input of blood glucose value, meal carbohydrate intake, and the reading of software dose recommendation: overall this took less than 10 s. Teletransmission of the data via the GPRS toward the website was automatic and instantaneous.

**CONCLUSIONS**—We included patients with chronic, poorly controlled type 1 diabetes despite an intensified insulin regimen. Use of the telemedicine Diabeo system led to a 0.9% decrease in HbA1c, compared with control. Improvements in HbA1c of this magnitude are rarely achieved in type 1 diabetes trials. For example, similar patients demonstrated a HbA1c improvement of only 0.6% after using a continuous blood monitoring device (8). We obtained a 10% reduction in the HbA1c level from baseline (−0.90%). Previous findings from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) studies suggest that such a 10% decrease in HbA1c levels could lead to a 39% reduction of retinopathy progression and 25% reduction in microalbuminuria onset in type 1 diabetes (9). Unlike the DCCT, this improvement was not associated with an increase in the frequency of hypoglycemia in the TeleDiab-1 Study.

Many telem medicine systems have been tested for type 1 or type 2 diabetes. They are based on the transmission of patient data, mainly blood glucose measurements, treatment, diet, or lifestyle, by telephone or Internet. Feedback from the diabetologist, nurse educator, or dietitian, for the adjustment of treatment, is then given, usually in a delayed manner, by telephone, SMS, or e-mail. The impact on HbA1c levels is often disappointing: a meta-analysis of nine randomized trials demonstrated a nonsignificant 0.11% decrease in HbA1c levels (10). Another study, pooling the data of six randomized trials, gave similar results (11). More recently, a meta-analysis incorporating new trials demonstrated statistically significant benefits, but with a modest average decrease in HbA1c levels (−0.21%) (12). These three meta-analyses involved a mix of type 1 diabetes and type 2 diabetes. When considering telecare in type 1 diabetes only, a meta-analysis including eight studies found no significant HbA1c improvement overall (13). Most of the systems were based on the electronic transmission of blood glucose data, with delayed and time consuming feedback by the medical staff.

Our large multicenter trial is the first study to show such a significant improvement in HbA1c using a telemedicine system in poorly controlled type 1 diabetes.

The Diabeo system also was beneficial regarding medico economic factors: G1 and G2 patients lost more than half a working day traveling for their hospital visit, whereas G3 patients saved time and money spent traveling to and from such visits; the total time spent consulting with the diabetologist did not differ from the time spent on usual care.
There are some limitations in our study. Because of the two components in the intervention with the Diabeo system—the software and the frequent contacts—two groups of patients were included in the study design. G2 patients who used the software without teleconsultations exhibited intermediate results, thus illustrating the part of the software per se; G3 patients showed what could be obtained with both. A study design including a fourth group with every 2 week contacts without the software would have been an interesting group in which to assess frequent phone contacts alone. But to be efficient, such an intervention would have required long duration telephone consultations to collect patient data. This would have been time consuming for the healthcare provider as demonstrated by Thompson et al. (14) and, thus, unrealistic.

Figure 2—Efficacy of electronic logbook ± teleconsultation. A: Glycated HbA1c mean values ± SE, from 3 months before baseline to month 6. *P = 0.0103, **P = 0.0019 compared with control group. B: Change in HbA1c, values (means ± SE) from baseline to month 6.
Even though HbA1c level decreased by an average of 0.9% in G3 patients, rather few patients (17%) achieved a satisfactory control with HbA1c <7.5%. This is because of the fact that the study has been conducted in patients with chronically poor glycemic control and high HbA1c value at baseline (9.07 ± 1.07%). One can expect better results in the subset of patients with HbA1c <8.0%, since it will be assessed in a large cohort study planned in France in the future.

Hypothetically, the success of the Diabeo® system is because of its two components: first, a real-time device for calculation of the insulin dose; and second, data transmission allowing telemonitoring and interactive short teleconsultations. Patients using both components had significantly lower HbA1c than control patients, regardless of the analysis carried out, for both the full population and limited to per-protocol data.

Improvement was not because of an increase in SMPG frequency. Interestingly, correlation between SMPG frequency and HbA1c was found only among G3 participants, suggesting that information provided by SMPG needs to be properly analyzed to influence HbA1c. Thus the main advantage of the Diabeo system is a correct interpretation of the data and an accurate calculation of the recommended insulin dose. Patient supported through short telephone consultations twice a month increased the beneficial impact of this system. These short and effective teleconsultations, focusing on adjustment of insulin therapy, were possible thanks to the ability to transmit complete and well-structured data.

This large multicenter trial is the first telemedicine study to show such a significant improvement in HbA1c using a telemedicine system in poorly controlled type 1 diabetes, without increasing medical time or expenses. Some telemedicine studies in insulin-treated patients have demonstrated significant HbA1c improvement but with large increases in the time devoted to telephone consultations (13,14). Other studies have focused on electronic transmission of blood glucose data but with ineffective delayed feedback (15,16) instead of real-time counseling for insulin dosage adaptation.

Patients considered for this study were a subset of patients with chronic, poorly controlled diabetes. Age or educational level was not predictive of success. Patients do not need to be young or have a high level of education to be able to use telemedicine systems such as Diabeo. However, patients need to be familiar with the smartphone and must be willing to use it. Best results were obtained with patients who wanted to continue with the system at the end of the study, despite having to pay for it. The question of the persistence of these results beyond 6 months and the extension of such results to other patient populations, with different ages, with lower educational level (56% had university degree and only 21% had “college or less” in our study), with less pump use, or with type 2 diabetes requiring basal-bolus regimen have to be assessed in a large cohort study that has been planned in France with a longer follow-up period.

Diabeo system is now available for the routine management of type 1 diabetes in France. Future improvements will incorporate food lists with pictures, to facilitate carbohydrate counting, which has been described for the Diabetes Interactive Diary. Use of this diary has recently been shown to improve some aspects of patients' QOL (17). The device’s reimbursement by healthcare insurance remains an obstacle in the telemedicine system diffusion. Our trial now provides a strong rationale for promoting the endorsement of such telemedical systems by insurance.

Acknowledgments—Voluntis provided the Diabeo software, and Orange (Paris, France) provided the smartphone and telephone lines; sanofi-aventis (Bridgewater, NJ) and CERITD funded the study. CERITD is a nonprofit clinical translational research center located in Corbeil Hospital (Corbeil-Essonnes, France). CERITD was fully involved in the design and coordination of the study. Voluntis, Orange, and sanofi-aventis were not involved in study design, data collection, or analysis. Study coordination, monitoring visits, data management, and entry from patient questionnaires and data analyses were performed independently by the Grenoble Clinical Research Centre, GC and the TeleDiab-1 scientific committee had full access to data and final responsibility for the content of the article. This study was sponsored by sanofi-aventis, Orange, and CERITD. Financial Disclosures are listed in the Supplementary Appendix. No other potential conflicts of interest relevant to this article were reported.

G.C. had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of data analysis, contributed to study concept and design, wrote the article, and obtained funding. P.-Y.B. contributed to study concept and design and to critical revision of the article; acquired, analyzed, and interpreted data; and wrote the article. D.D. contributed to study concept and design and analyzed data. A.C. acquired data and contributed to the critical revision of the article. S.F. contributed to study concept and design and wrote the article. P.S.-B. acquired data and contributed to the critical revision of the article and to administrative, technical, or material support. B.C. acquired data and contributed to the critical revision of the article. V.M. contributed to study concept and design and to critical revision of the article and acquired data. L.C. acquired, analyzed, and interpreted data and contributed to the critical revision of the article. The authors would like to thank Lydie Canipel from CERITD for assistance to the TeleDiab-1 Study Group and Myriam Haddouche and Carole Rolland from CIC-INSERM, Grenoble University Hospital, for involvement in the management of the study.

References

1. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002;325:746
real-time continuous glucose monitoring. Diabetes Care 2006;29:2730–2732