Use of telemedicine in subjects with type 1 diabetes equipped with an insulin pump and real-time continuous glucose monitoring

Inmaculada González-Molero*, Marta Domínguez-López*, Mercedes Guerrero*, Mónica Carreira†, Felix Caballero‡, Eleazara Rubio-Martín*, Francisca Linares*, Isabel Cardona§, María Teresa Anarte†, María Soledad Ruiz de Adana* and Federico Soriguer*

*Endocrinology and Nutrition Service, Carlos Haya Hospital and CIBERDEM (Instituto de Salud Carlos III), Málaga, Spain; †Personality, Evaluation and Psychological Treatment, Psychology Faculty, Málaga University, Spain; ‡Psychiatric Department, Autonomous University of Madrid, Spain; §Endocrinology and Nutrition Service, Hospital Virgen de La Victoria, Málaga, Spain

Summary
We evaluated a telemedicine system in patients with type 1 diabetes who had optimized treatment with an insulin pump and a real-time continuous glucose monitoring system. We conducted a prospective, one-year study of 15 subjects. Three medical visits took place: pre-baseline, baseline and at 6 months. Each month the subjects transmitted information from the glucose meter, glucose sensor and insulin pump. We adjusted the treatment and returned the information by email. We evaluated psychological and metabolic variables, including HbA1c, hypoglycaemia, hyperglycaemia and glucose variability. At baseline the mean age of the subjects was 40 years and the mean duration of diabetes was 22 years. There was a significant reduction in HbA1c (7.50 to 6.97%) at 6 months, a significant increase in the number of self-monitoring blood glucose checks per day (5.2 to 6.2), and significant improvements in variability: MODD, mean of daily difference (67 to 53) and MAGE, mean amplitude of glycaemic excursions (136 to 102). There were significant improvements in quality of life (92 to 87), satisfaction with the treatment (34 to 32) and less fear of hypoglycaemia (36 to 32). Adult subjects with type 1 diabetes on treatment with a continuous insulin infusion system and a real time glucose sensor and who have acceptable metabolic control and optimized treatment can benefit from the addition of a telemetry system to their usual outpatient follow-up.

Introduction
Diabetes is a chronic disease which requires rapid and frequent therapeutic adjustments, and in which good metabolic control reduces complications and mortality.1 Several studies have evaluated the effect of incorporating a telemedicine system for the follow-up of patients with diabetes. However, numerous factors have led to difficulty in drawing generalized conclusions, such as the study population (type 1 or type 2 diabetes, treated with insulin or with oral anti-diabetic agents), the variety and diversity of the study designs, different inclusion criteria, and the measurement of different endpoints and variables. Some studies in adults with type 1 diabetes have failed to show any improvement in glycaemic control compared to controls,2,3 although other studies have done so.4,5

Treatment with a subcutaneous insulin pump is effective for the metabolic control of subjects with type 1 diabetes, reducing HbA1c and the number of hypoglycaemic episodes without increasing the risk of ketoacidosis and thus improving the subject’s quality of life.6,7 Continuous glucose monitoring systems also improve metabolic control in subjects with type 1 diabetes.8

Very few studies have evaluated the long-term effect of telemedicine in subjects with type 1 diabetes treated with a subcutaneous insulin pump and a real-time continuous glucose monitoring system.5 The aim of the present study was to evaluate the overall effect of adding a telemedicine system in adult subjects with type 1 diabetes treated with a
subcutaneous insulin pump and real-time continuous glucose monitoring.

Methods

The study was conducted on 15 therapeutically homogeneous patients with type 1 diabetes mellitus, all treated for more than 1 year with a subcutaneous insulin pump and an integrated real-time continuous glucose monitoring system (Paradigm real-time PRT, Northridge, CA, USA), with HbA1c < 8% and normal renal function. The subjects were followed up for 1 year and monitored exclusively by telemetry during the last 6 months of this period. During the first 6 months, the subjects were provided with the telemetry material and given instructions about its use. The participants made 3 outpatient visits: at the start of the study, i.e. 6 months before beginning the telemetry period (pre-baseline), just before starting the telemetry period (baseline), and 6 months after initiating the telemetry period (6-month visit).

Each month during the 6-month telemetry period, the subjects sent via the Internet (Medtronic Carelink-Pro, Northridge, CA, USA) information from the insulin pump (Paradigm 722, Northridge, CA, USA), the real-time sensor (Minilink, Northridge, CA, USA) and the glucose meter (Bayer Contour meter, Basel, Switzerland). Subjects received a medical response by email within 48 hours, informing them of the treatment changes to be made (e.g. insulin adjustments, number and time of checks with a glucose meter, nutrition advice, remember how to proceed with hyper- and hypoglycaemia and solve other problems that subjects had with their control, continuous subcutaneous insulin infusion or sensor). At the outpatient visits, the same treatment adjustments were made, and a physical examination was performed with measurements of bodyweight, height, waist and hip circumferences, impedance meter data and blood pressure.

Laboratory studies were also made of blood glucose, HbA1c, biochemistry, blood and clotting variables. The subjects collected a 24-h urine sample for later analysis. At pre-baseline, baseline and at 6 months a psychological evaluation was carried out, with measurement of the following variables:

(1) DQOL = Diabetes Quality of life (Spanish version);
(2) DQOLPR = Social/vocational concerns;
(3) DQOLINSAT = Dissatisfaction with the treatment;
(4) DQOLIMP = Impact of the treatment;
(5) FH = Fear of hypoglycaemia;
(6) STAIE = Anxiety state;
(7) STAIR = Anxiety traits (State-Trait Anxiety Inventory Form);
(8) BDI = Depression (Beck Depression Inventory).

The information obtained monthly from the pump, sensor and glucose meter included the following: mean blood glucose and SD, duration of hyperglycaemia, normoglycaemia and hypoglycaemia, area under the curve below 70 and above 140 mg/dl, number of mild hypoglycaemic episodes (blood glucose < 70 mg/dl) and severe episodes (hypoglycaemic episodes requiring action by a different person), number of hyperglycaemic episodes (glycaemia > 250 mg/dl, hospital admission due to acute decompensation (ketoacidosis and severe hypoglycaemia), number of self-controls (checks with a glucose meter) per day, time wearing the sensor per month, insulin dose (ratio boluses/basal insulin and Units/kg of bodyweight), number of boluses per day (as an indicator of treatment adherence), number of days with fewer than 3 boluses and percentage of computer-suggested/conventional boluses. Calculations were made of the sensitivity factor (quantity of glucose which is lowered by 1 U of insulin: 1800/total insulin dose), insulin:carbohydrate ratio (quantity of carbohydrates covered by 1 U of insulin: 500/total insulin dose) and measurements of glucose variability: the SD of the glucose meter and sensor, MAGE (mean amplitude of glycaemic excursions) with capillary glucose, MODD (mean of daily difference) with interstitial glucose; measures of risk of extreme values: LBGI (low blood glucose index), HBGI (high blood glucose index), BGRI (blood glucose risk index) and GRADE (Glycaemic Risk Assessment Diabetes Equation) based on the interstitial glucose of 5 consecutive days.

We used the Wilcoxon signed-rank test to analyse the possible differences occurring during the study. The Mann–Whitney U test was used to evaluate the differences between two independent groups (subjects with and without complications) and to evaluate Spearman’s correlation coefficients.

The study was approved by the appropriate ethics committee.

Results

Of the 15 subjects initially included in the study, two were lost during follow-up (one due to intention to become pregnant and the other due to inability to handle the telemetry device). The characteristics of the subjects at the time of inclusion are shown in Table 1.

Metabolic control and therapeutic adherence

The mean plasma HbA1c levels were significantly lower at the 6-month visit compared with the pre-baseline level, see Table 2. There were no significant changes between the

<table>
<thead>
<tr>
<th>Table 1 Characteristics of the patients at the time of inclusion in the study (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
</tr>
<tr>
<td>No of males/females</td>
</tr>
<tr>
<td>Duration of the diabetes, years (SD)</td>
</tr>
<tr>
<td>No of patients treated with the infusion system</td>
</tr>
<tr>
<td>and glucose sensor for longer than 1 year</td>
</tr>
<tr>
<td>HbA1c at pre-baseline, % (SD)</td>
</tr>
</tbody>
</table>
three visits in the periods of hyperglycaemia, normoglycaemia or hypoglycaemia, in the number of mild hypoglycaemic episodes per week, in the area under the curve below 70 or above 140 mg/dl, in the number of severe hypoglycaemic episodes or in ketoacidosis at 6 months (Table 2). Regarding adherence, there were no significant changes in the mean time per day with the sensor and the number of days with omission of insulin boluses, the overall number of boluses per day or the proportion of manual boluses to computer-suggested boluses. The number of self-controls rose at the 6-month visit compared with the pre-baseline visit (Table 2). There was a reduction in insulin units per kg of bodyweight and a significant increase in insulin ratio and sensitivity, with no significant changes in bodyweight throughout the study.

Concerning glucose variability, there was a significant reduction in the MODD at 6 months compared to both pre-baseline and baseline (53.1 vs. 68.7; \( P < 0.05 \) and 53.1 vs. 67.3; \( P < 0.05 \)) and in the MAGE (102.4 vs. 144.4; \( P < 0.05 \) and 102.4 vs. 136.3; \( P < 0.05 \)). No significant changes occurred in the other measures of variability (SD, LBGI, HBGI, GRADE).

At 6 months, the mean value of the glucose meter and the sensor (\( r = 0.72; P = 0.008 \)) and the SD of the glucose meter and the sensor (\( r = 0.72; P = 0.09 \)), correlated significantly. The time with the sensor correlated positively with the time in normoglycaemia (\( r = 0.59; P = 0.04 \)) and negatively with the number of mild hypoglycaemic episodes per week (\( r = -0.64; P = 0.03 \)). The correlation between the different measurements of variability and metabolic control is shown in Table 3.

### Psychological variables

There was an improvement in the score of quality of life at 6 months compared to the pre-baseline evaluation (92.4 vs. 86.9; \( P = 0.012 \)). The differences were not significant between pre-baseline and baseline, nor between baseline and 6 months. No overall significant differences were found in the subscales DQOLINSAT, DQOLPR, DQOLIMP, fear of hypoglycaemia, anxiety state, anxiety traits or depression. Separating the subjects with good and poor glycaemic control (plasma HbA1c above/below 7%) showed that the subjects with poor glycaemic control experienced a significant improvement between the baseline study and the 6-month study in the variable dissatisfaction with treatment (34.3 vs. 31.6; \( P = 0.02 \)) and a reduction in fear of hypoglycaemia (35.6 vs. 31.6; \( P = 0.018 \)). Studying separately the subjects with and without chronic complications showed that the subjects without these complications experienced an improvement in quality of life (87.2 vs. 79.5; \( P = 0.02 \)) and in the subscale dissatisfaction with treatment (33.4 vs. 30.4; \( P = 0.04 \)). In the group of subjects who had complications, there were no significant differences at the 6-month visit in any of the psychological variables studied.

### Oxide reduction parameters

There were significant differences in 8-isoprostanoid F2 alpha in 24-h urine samples between the pre-baseline (963 pg/mg) and six months (787 pg/mg) mean values \( P < 0.04 \). No correlation was found in the levels of

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**Table 2** Metabolic control and therapeutic adherence

<table>
<thead>
<tr>
<th></th>
<th>Pre-baseline</th>
<th>Baseline</th>
<th>6 months</th>
<th>( P )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, % (SD)</td>
<td>7.50 (0.59)</td>
<td>7.24 (0.58)</td>
<td>6.97 (0.49)</td>
<td>0.011</td>
</tr>
<tr>
<td>Percentage of time in hypoglycaemia (SD)</td>
<td>13.9 (9.4)</td>
<td>18.4 (13.1)</td>
<td>16.5 (10.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Percentage of time in hyperglycaemia (SD)</td>
<td>46.1 (11.9)</td>
<td>42.9 (17.3)</td>
<td>44.3 (15.4)</td>
<td>NS</td>
</tr>
<tr>
<td>No of mild hypoglycaemic episodes per week (SD)</td>
<td>4.4 (3.0)</td>
<td>4.3 (3.2)</td>
<td>3.2 (1.9)</td>
<td>NS</td>
</tr>
<tr>
<td>AUC 70 (SD)</td>
<td>0.81 (0.81)</td>
<td>0.83 (1.12)</td>
<td>0.53 (0.66)</td>
<td>NS</td>
</tr>
<tr>
<td>AUC 140 (SD)</td>
<td>15.3 (8.3)</td>
<td>22.8 (8.1)</td>
<td>20.2 (10.4)</td>
<td>0.006*</td>
</tr>
<tr>
<td>No of self-controls, per day (SD)</td>
<td>5.1 (1.4)</td>
<td>5.8 (1.3)</td>
<td>6.2 (2.0)</td>
<td>0.034</td>
</tr>
<tr>
<td>Time with the sensor, hours per day (SD)</td>
<td>14.2 (4.8)</td>
<td>16.2 (4.1)</td>
<td>14.3 (5.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Days with fewer than 3 boluses (SD)</td>
<td>2.8 (4.4)</td>
<td>3.1 (4.9)</td>
<td>4.4 (7.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Denotes \( P < 0.05 \)

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**Table 3** Correlation between measures of variability and metabolic control

<table>
<thead>
<tr>
<th></th>
<th>Mean glucose meter</th>
<th>Mean glucose sensor</th>
<th>SD glucose meter</th>
<th>SD sensor</th>
<th>MAGE</th>
<th>HBGI</th>
<th>LBGI</th>
<th>MODD</th>
<th>AUC140</th>
<th>AUC70</th>
<th>Time in hyperglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean glucose sensor</td>
<td>0.76*</td>
<td></td>
<td>0.72*</td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD glucose meter</td>
<td>0.72*</td>
<td>0.52</td>
<td>0.72*</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD sensor</td>
<td>0.52</td>
<td>0.72*</td>
<td>0.37</td>
<td>0.79*</td>
<td>0.69*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAGE</td>
<td>0.57</td>
<td>0.37</td>
<td>0.79*</td>
<td>0.69*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBGI</td>
<td>0.73*</td>
<td>0.78*</td>
<td>0.68*</td>
<td>0.72*</td>
<td>0.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBGI</td>
<td>-0.79*</td>
<td>-0.65*</td>
<td>-0.41</td>
<td>-0.27</td>
<td>-0.28</td>
<td>-0.56*</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MODD</td>
<td>0.27</td>
<td>0.37</td>
<td>0.65*</td>
<td>0.68*</td>
<td>0.40</td>
<td>-0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC140</td>
<td>0.67*</td>
<td>0.94*</td>
<td>0.62</td>
<td>0.86*</td>
<td>0.48</td>
<td>0.85*</td>
<td>-0.48</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC70</td>
<td>-0.53</td>
<td>-0.70*</td>
<td>-0.28</td>
<td>-0.25</td>
<td>-0.11</td>
<td>-0.27</td>
<td>-0.78*</td>
<td>0.18</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in hypoglycaemia</td>
<td>0.52</td>
<td>0.57</td>
<td>0.52</td>
<td>0.41</td>
<td>0.45</td>
<td>0.63*</td>
<td>-0.83</td>
<td>0.38</td>
<td>0.49</td>
<td>-0.64*</td>
<td></td>
</tr>
<tr>
<td>Time in hyperglycaemia</td>
<td>-0.39</td>
<td>-0.47</td>
<td>-0.39</td>
<td>-0.13</td>
<td>-0.25</td>
<td>-0.42</td>
<td>0.83*</td>
<td>-0.12</td>
<td>-0.38</td>
<td>0.69*</td>
<td>-0.79*</td>
</tr>
</tbody>
</table>

* Denotes \( P < 0.05 \)
8-isoprostanoid F2 alpha and mean glucose of the glucose meter or sensor, plasma HbA1c or any index of glucose variability.

Discussion

Despite the increasing use of telemedicine in patients with diabetes, the usefulness of these systems requires evaluation in different groups of subjects according to the type of diabetes and the treatment. We undertook a pilot study in a therapeutically homogeneous group of subjects with type 1 diabetes treated with an insulin pump and a real-time continuous glucose monitoring system for over 1 year. There was a significant reduction in HbA1c compared with pre-baseline values, suggesting that knowing they were going to be involved in a study and be observed resulted in the subjects improving their control. In addition, between the baseline and the 6-month studies there was a further reduction in HbA1c with no increase in the number of hypoglycaemic or hyperglycaemic episodes. Earlier studies of the effect of telemedicine on HbA1c levels produced very different results: adults with type 1 diabetes experienced an improvement4,5,9 in some studies although in other studies the reduction was similar to that in the control groups.2,3

In agreement with earlier studies,3,9,10 no increase was seen in the number of episodes of acute decompensation (ketoacidosis or severe hypoglycaemia) in spite of not visiting the clinic for 6 months.

At the baseline visit in our study, the mean number of days per month with fewer than three insulin boluses was 2.8, while during the telemetry follow-up no significant decrease was seen in the number of days with bolus omission. Regarding the time with the sensor, although the subjects were initially instructed to maintain the sensor the whole time, the mean was 14.2 hours per day. In the STAR 3 study an increased frequency of sensor use was associated with a greater reduction in glycaemic haemoglobin levels.11 In our study there was a reduction in the HbA1c wearing the sensor 59% of the time, and the time with the sensor correlated positively with the time in normoglycaemia and negatively with the number of mild hypoglycaemic episodes per week. The number of self-controls increased significantly. This increase has been reported previously.12

Growing evidence suggests that the reduction in glucose variability should be an independent aim in subjects with diabetes, due to its effect on the production of free radicals and oxidative stress.13 Various methods have been proposed for its calculation, although no gold standard yet exists for its measurement. The HBGI and LBGI indexes were developed by Kovatchev et al.14 The former index is a measurement of the frequency and extension of the readings of low blood glucose levels, based on the hyperglycaemic section of the blood glucose risk space. Similarly, the latter index calculates the frequency and extension of the readings of high blood glucose levels.

Kovatchev et al. defined BGRI (sum of the LBGI and HBGI) as an overall measure of risk, based on the risk for hypoglycaemic and hyperglycaemic episodes. In our subjects we recorded a moderate risk of hyperglycaemia and hypoglycaemia that did not change significantly throughout the follow-up.

GRADE is an index defined by Hill et al.15 from which the expected percentage of hypoglycaemia, hyperglycaemic and normoglycaemic episodes can be obtained. In our subjects no significant differences were found between the respective evaluations in the three percentages. MAGE is an index of the intra-daily variation around a mean glucose level adding the absolute values of the rises and falls throughout one day.16 MODD, an index of inter-daily variation,17 is the mean absolute value of the differences between glucose values on two consecutive days at the same time of day. A modified MODD permits its use for many days. In our subjects a significant reduction was found in the intra-daily glucose variability, as measured with MAGE, and the inter-daily variability, measured by calculating the MODD for five consecutive days. These findings are in agreement with the reduction in glucose variability and postprandial glycaemia reported in earlier studies with a telemetry follow-up with and without an insulin pump.18

In the various parameters of variability, we found a significant positive correlation between MODD and MAGE, that is between the intra-daily glucose variability calculated with capillary glucose values and the inter-daily variability, calculated from the 5-day interstitial glucose levels. As previously described,19 a good correlation was also seen between the other measures of variability of the glucose meter and the sensor.

The subjects studied experienced a general improvement in quality of life between the pre-baseline point and the 6-month visit and the subgroup of subjects with HbA1c >7% showed increased satisfaction with their treatment after setting up the telemetry system. Some earlier studies have reported improvements in quality of life, anxiety, depression and treatment satisfaction19 in subjects with type 1 diabetes, type 2 diabetes and pregnant women. However, ours is the first study to find a reduction in the fear of hypoglycaemia after starting to use a telemetry system.

The metabolite 8-isoprostanoid F2 alpha is a good marker of oxidative stress.20 Several studies have examined the levels of 8-isoprostanoid F2 alpha in 24-h urine samples from subjects with diabetes in comparison with persons without diabetes, finding higher levels in subjects with type 1 or type 2 diabetes than in controls.21,22 Nevertheless, studies of its relation with HbA1c have given differing results: it has been correlated with HbA1c in some studies,23 but not in others.21 We found no correlation with mean glucose or HbA1c. Concerning its relation with glucose variability, no correlation was found in our group of subjects with any of the variables studied, similar to the findings of two earlier studies in subjects with type 1 diabetes.22,23 In type 2 diabetes, however, a correlation has been found in subjects treated with oral anti-diabetic agents, though not in
subjects treated with insulin. These differences may be due to the different methods used for measurement, or due to the effect of insulin therapy on oxidative stress.

Our study had certain strengths and limitations. It was the first study to evaluate the effect of telemetry in a group of subjects with a continuous insulin infusion system and a real time glucose sensor over a 6-month period and involving an initial optimization period, which therefore eliminated the possibility of a Hawthorne effect. In addition, the study examined various outcome variables, measuring the overall effect of the establishment of the system. The main limitations of the study concern the lack of a control group and the reduced sample size, which was the result of seeking a therapeutically homogeneous and well optimized group.

Thus, we conclude that adult subjects with type 1 diabetes on treatment with a continuous insulin infusion system and a real time glucose sensor and who have acceptable metabolic control and optimized treatment can benefit from the addition of a telemetry system to their usual outpatient follow-up, experiencing additional improvements in their HbA1c, glucose variability and quality of life, as well as a reduction in their fear of hypoglycaemia. However, more extensive studies must be done to confirm these preliminary results.

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