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Amelioration of user experiences and glycaemic outcomes with an Advanced Hybrid Closed Loop System in a real-world clinical setting.

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Opposed Reviewers:	
Response to Reviewers:	Dear Professor Ceriello, Thanks for allowing us to revise our manuscript. We thank the reviewers for their comments. We have looked into them in detail and all the changes and suggestions have been included in the revised manuscript as detailed. Reviewer 1: Comment: I appreciate the effort to respond to each of the comments proposed in the previous revisions as well as to include the suggested changes. With respect to the latest revision, most of the authors' responses to the comments made seem to me to be adequate. However, I would like to point out that on page 6 in the sentence "The subjects were asked to complete, at baseline....., in their Spanish validated versions", the word "subjects" should be replaced by "participants". Likewise, although a Spanish version of the DDS is available, the authors do not refer to any previous

	study in which its validity has been tested in a sample of people with diabetes in Spain. Therefore, in order not to confuse the reader, it would be more appropriate to eliminate the phrase "...in their Spanish validated versions" since it is not applicable to the case of the DDS, although it is applicable to the rest of the measures used (ref. 28, 33, 35....). Answer: Thank you for your comment. The word “subjects” has been replaced by “participants” and the sentence “in their Spanish validated versions” has been eliminated.

Title

Amelioration of user experiences and glycaemic outcomes with an Advanced Hybrid Closed Loop System in a real-world clinical setting.

Running title: Satisfaction with Medtronic MiniMed 780G system

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Abstract

Aims. Automation in diabetes technology is rapidly evolving. The aim was to evaluate the real-world glycemic outcomes and user acceptance after 3 months of using the Medtronic 780G Advanced Hybrid Closed-Loop (AHCL) system.

Methods. A prospective analysis was performed. A glucose target of 100 mg/dl and an active insulin time of 2 hours were set. Capillary HbA1c, 2-week of pump and sensor data and several satisfaction questionnaire scores were compared at baseline and after 3 months of using the AHCL system.

Results. 52 subjects were selected (age: 43±12 years, sex: 73% female, diabetes duration: 27±11 years, higher education: 31%). Time in range (TIR) 70-180 mg/dl increased from 67.3±13.6% to 80.1±7.5% and time >180 mg/dl and >250 mg/dl were reduced (16.8±8.4 *vs* 29.4±15.1%, 2.7±3.0% *vs* 6.9±7.8%, respectively) (all $p<0.001$), while time in hypoglycaemia remained below recommended targets. Time in Auto-Mode and sensor use were 94±10% and 90±11%, respectively. Auto-correction boluses represented 29±12% of bolus insulin. Fear of hypoglycaemia, diabetes quality of life, sleep quality and satisfaction with the monitoring system improved after 3 months.

Conclusion. The real-world use of the AHCL system Medtronic 780G provides an 80.1% TIR 70-180 mg/dl with minimal hypoglycaemia and an increased level of patient satisfaction.

Keywords: type 1 diabetes, advanced hybrid closed loop system, patient satisfaction.

Introduction

The use of different technology options has become the standard of care for the management of people with type 1 diabetes (T1D). Consecutive advances in the automation of the systems have led to a reduction in time in hypoglycaemia and an increase in time in range between 70 mg/dl and 180 mg/dl (TIR 70-180 mg/dl). The low-glucose suspend function was the first automation in sensor-augmented pumps and it was followed by the predictive low-glucose suspend feature (SAP-PLGS) [1].

The latest automated insulin infusion systems, so-called closed-loop systems or artificial pancreas systems, include control algorithms that continuously decide the infusion of insulin according to real-time glucose sensor values. International consensus recommends a 70% TIR 70-180 mg/dl as the target for people with T1D [2, 3] and artificial pancreas were the first systems to allow the majority of patients to reach that 70% target [4]. Also, these systems have been shown to offer the maximum benefit in a real-world setting [5,6].

With the evolution of automation in diabetes technology, improvement in TIR 70—180 mg/dl has been accompanied by a higher level of patient satisfaction [7-11]. In this context, several aspects of the user experience with closed-loop systems are recognised to impact patient-reported outcomes. Maintaining the patient as close as possible to normoglycaemia, by avoiding hyperglycaemia while minimising hypoglycaemia is one of the main goals of automated insulin delivery; consequently, a reduction in fear of hypoglycaemia and an increased feeling of safety are expected after the introduction of a closed-loop system. Also, the glucose sensor is an essential component of closed-loop systems; its accuracy, the number of alerts it generates and

its calibration requirements should have an impact int the overall patient satisfaction with the system. In addition, changes in sleep quality might be expected after the implementation of a closed-loop system; first, the improvement in glycaemic control could reduce the number of nocturnal hyperglycaemia and hypoglycaemia episodes, having a positive impact on sleep quality; on the other hand, the possible alerts generated by the system requirements or malfunctions could harm patient sleep. All these aspects together would probably have a deep impact on the overall quality of life in closed-loop system users. Validated and reliable tools to assess the relevant perceived benefits and burdens in relation to automated insulin delivery systems are being developed [12].

The mentioned psychological impact of the use of closed-loop systems has been previously evaluated in clinical trials [10, 11, 13-21]. Patients' preferences and views regarding the use of closed-loop systems have been assessed through interviews, psychological questionnaires and online surveys in adults, adolescents, children and parents. Overall, the level of satisfaction and acceptance of closed-loop systems has been reported to be high. The main positive remarks refer to less diabetes burden and distress, improved glycaemic control, better sleep quality, improved general well-being and quality of life and reduction in worries about hypoglycaemia and hyperglycaemia. The key negative points expressed by the users are technical difficulties and connectivity issues, discomfort, the intrusiveness of alarms and the devices wearability.

The Advanced Hybrid Closed-Loop (AHCL) system Medtronic MiniMed 780G was launched in Europe in October 2020. This system automatically infuses insulin according to interstitial sensor glucose values, to different glucose targets (100, 110 or 120 mg/dl) and it also delivers

auto-correction boluses to a glucose target of 120 mg/dl. Precommercial studies showed an increase in TIR 70-180 mg/dl from 5.7% to 12.5% in different groups of patients [22-24].

We have previously reported a preliminary analysis showing the rapid improvement in glycaemic control achieved in the first 30 days after the initiation of the 780G system, showing a 12.3% improvement in TIR 70-180 mg/dl from day 1 [25]. The aim of this study was to evaluate the real-world benefits of the Medtronic 780G AHCL system, in terms of glycaemic control and of patient acceptance, after 3 months of use, in the same group of patients.

Material and Methods

A longitudinal prospective protocol was designed. Patients using the SAP-PLGS Medtronic 640G system were simultaneously upgraded to the AHCL Medtronic 780G system. Pregnant patients were not included. The study subjects participated in a training session to start the system in Manual Mode and to explain its functioning. One week later, another training session was scheduled to explain the Auto-Mode and initiate its use. The duration of both training sessions was 3 hours. The bolus calculator settings were programmed equally to the previous configuration. An active insulin time of 2 hours and a glucose target of 100 mg/dl was programmed for all the patients, according to protocol. All the patients had the auto-correction bolus function activated.

At baseline and after 3 months of use of Auto-Mode, several variables were recorded, including weight, height and capillary HbA1c, measured by Afinion^{TM}. Two-week of sensor and

insulin data were downloaded for the system, both the 640G, at baseline and the 780G, at 3 months. The following data were collected from the downloads: TIR 70-180 mg/dl, time < 54 mg/dl and < 70 mg/dl, time > 180 and > 250 mg/dl, sensor use, mean glucose sensor levels, standard deviation of sensor glucose, coefficient of variation of sensor glucose, total daily insulin dose, number of SMBGs per day and sensor use. Variables related to the use of the system at the end of follow-up were also assessed, including time in Auto-Mode, the number of exits from Auto-Mode per week and the reasons for these exits, the amount of insulin given as autocorrection boluses and the number of calibrations.

The participants were asked to complete, at baseline and at the 3-month visit, the following questionnaires: Hypoglycaemia Fear Survey (HFS) to evaluate fear of hypoglycaemia [26-28], Glucose Monitoring Experience Questionnaire (GME-Q) to assess satisfaction with the glucose monitoring system [29, 30], Gold and Clarke scores to analyse hypoglycaemia awareness [31-33], Diabetes Quality of Life (DQoL) for quality of life assessment [34, 35], Diabetes Distress Scale (DDS) to measure diabetes-related stress [36, 37], diabetes satisfaction with the treatment (DST) [38, 39] and Pittsburgh Sleep Quality Index to evaluate sleep quality (PSQI) [40, 41].

In summary, The HFS comprises 33 items, grouped in 2 subscales, behaviour subscale and worry subscale, with 5 possible answers por each question, to sum a global score; higher scores represent increased fear of hypoglycaemia. The GME-Q includes 23 items, with 3 subscales (effectiveness, intrusiveness, convenience), with a 5-point Likert scale; higher scores indicate higher satisfaction with the monitoring system. The Gold score evaluates hypoglycaemia awareness with a single question about hypoglycaemia awareness, that the patient has to rate

from 1 to 7; the Clarke score is formed of 8 questions, with different possible answers; in both cases, a score > 3 reflects impaired awareness of hypoglycaemia. The DQoL questionnaire has 42 questions, grouped in 4 subscales (patient satisfaction, impact generated by diabetes, worry about diabetes and social worry), with 5 possible answers, and higher scores indicate a poorer quality of life. The DDS is formed by 17 items, with a 6-point Likert scale, and higher scores represent higher distress. The DST questionnaire is comprised of 8 items, with a 0 to 6 scale, and higher scores represent higher satisfaction with the diabetes treatment. The PSQI questionnaire includes 19 items, with a 0 to 3 scale; higher scores represent poorer sleep quality; a score > 5 is considered a poor sleep quality.

Also, the following open questions were asked to the patients to assess their general satisfaction with the system: *what is s your opinion on the 780G system? what has been improved in the 780G system, compared to the 640G system? what is worse in the 780G system, compared to the 640G system? has your glycaemic control improved? do you have more hypoglycaemic events? do you find it easier to control your diabetes? do you get more or fewer alerts? do you sleep better or worse? what would you improve in the 780G system?*

The study protocol followed the Declaration of Helsinki principles and was approved by the Badajoz University Hospital Ethics Committee (date: 22 October 2020). All the participants were informed of the protocol and signed a consent form.

Data analysis was performed using the SPSS statistics software v22. Results are presented as mean ± SD values. A paired Student's t-test was used for the analysis of differences. For unpaired samples, the independent samples t-test was used. A McNemar test was used to

compare proportions for paired data. Correlation analyses were performed using the Pearson correlation coefficient. A p-value < 0.05 was considered statistically significant.

Results

52 people with T1DM were included in the study. Demographic characteristics were as follows: age: 43 ± 12 years (15-65), 10% (n = 5) adolescents and young adults (< 21 years old), sex: 73% (n = 38) female, diabetes duration: 27 ± 11 years, BMI: 25 ± 5 kg/m^2, higher education: 31% (n = 16), time on pump: 6.5 ± 3.4 years, time on SAP-PLGS: 4.6 ± 2.2 years.

Glycaemic outcomes.

The outcomes after 3 months of use of the AHCL system, compared to the outcomes at baseline, with the SAP-PLGS system, are summarised in Table 1. An increase of TIR 70-180 mg/dl from 67.3 ± 13.6% to 80.1 ± 7.5% was found (p < 0.001), with a range of TIR 70-180 mg/dl from 59% to 94% at 3 months. Also, HbA1c decreased from 56 ± 10 mmol/mol to 49 ± 7 mmol/mol (7.23 ± 0.86% to 6.67 ± 0.61%) (p < 0.001).

The percentage of patients with HbA1c ≤ 53 mmol/mol (7%) increased from 46% (n = 24) at baseline to 67% (n = 35) at 3 months (p = 0.001). The percentage of patients with TIR 70-180 mg/dl > 70% increased from 46% (n = 24) at baseline to 89% (n = 46) at 3 months (p < 0.001). The 6 patients who did not reach the target of TIR 70-180 mg/dl > 70% had a TIR 70-180 mg/dl of 59%, 65%, 67%, 68% and 70% (2 patients). The percentage of patients with TIR 70-180 mg/dl > 70% and time < 70 mg/dl < 4% increased from 31% (n = 16) at baseline to 60% (n = 31) at 3

months (p = 0.001). No severe hypoglycaemia or diabetic ketoacidosis episodes occurred during follow-up.

Four patients were diagnosed with SARS-CoV-2 infection and were confined for 14 days. Neither of them required hospitalization due to infection severity or to deterioration of glycaemic control, and the system was maintained in Auto-Mode during the infection.

Use of the system.

The parameters reflecting the functioning of the AHCL system after 3 months of use are detailed in Table 2. A significant amount of auto-correction boluses was administered by the system, representing 29 ± 12% of the percentage of bolus insulin, with a wide range (from 10% to 68%). A significant negative correlation was found between TIR 70-180 mg/dl and the percentage of insulin delivered as auto-correction boluses ($r = -0.704$, $p < 0.001$).

When evaluating the system settings at 3 months, 94% (n = 49) of the participants had maintained the glucose target of 100 mg/dl and an active insulin time of 2 hours during the 3 months of study. Two patients had switched their glucose target to 110 mg/dl, due to high hypoglycaemia frequency. An additional patient had increased the glucose target to 110 mg/dl and the active insulin time to 3 hours, due to extreme fear of hypoglycaemia, without actually having experienced hypoglycaemia episodes. All 52 subjects kept the auto-correction function activated. No changes were seen in the grams of carbohydrate to insulin ratios programmed in the system for any of the meals.

The main reason for the system exiting from Auto-Mode to Manual Mode was "SmartGuard deactivated by the user" (31%) followed by "end of sensor life" (19%), "no calibration" (17%) and "sensor update" (16%). The rest of the reasons were uncommon (less than 8%).

The number of hyperglycaemia alarms was reduced from 2.8 ± 3.2 to 1.9 ± 1.8 alarms per day (p = 0.037), while the number of hypoglycaemia alarms increased from 2.5 ± 2.6 to 3.5 ± 3.0 alarms per day (p = 0.007).

Patient-reported outcomes.

The Clarke score was reduced from 2.49 ± 1.9 at baseline to 2.14 ± 2.0 at the 3-month visit (p = 0.04). The Gold score was not significantly reduced (3.5 ± 1.7 at baseline *vs* 3.1 ± 2.0 at the 3-month visit ; p = 0.084). The changes in the scores in the different questionnaires regarding patient-reported outcomes are shown in Figure 1 in box plots, representing median, maximum, minimum and 25^{th} and 75^{th} percentiles. Regarding fear of hypoglycaemia, although HFS score was significantly reduced after 3 months (46 ± 25 at baseline *vs* 37 ± 23 at 3 months, p = 0.002), reflecting a reduction in fear of hypoglycaemia, this difference was due to an improvement in the behaviour subscale (19 ± 11 at baseline *vs* 14 ± 10 at 3 months, p = 0.002), while the changes in the worry subscale were not significant (26 ± 18 at baseline *vs* 22 ± 18 at 3 months, p = 0.072). Diabetes quality of life, evaluated by the DQoL questionnaire, showed a decrease in the score at 3 months, compared to baseline (81 ± 21 at baseline vs 76 ± 16 at 3 months, p = 0.036), meaning better quality of life. The GME-Q score increased, from 3.8 ± 0.4 to 4.0 ± 0.4, p = 0.007, reflecting a better experience with the glucose sensor. Also, a lower PSQI score was seen with the AHCL

system compared to baseline (5.8 ± 3.5 *vs* 6.6 ± 3.8, p = 0.047), reflecting a better sleep quality. No differences were found in the DST or DDS scores.

One patient (male, 25 years old, engineer) decided to stop using the Auto-Mode after 4 days of use, despite a better glycaemic control (85% TIR 70-180 mg/dl *vs* 67% at baseline) as he preferred to be able to manually adjust the insulin infusion, and he was excluded from the analysis. The rest of the patients expressed their desire to continue using the system.

The score in the first question in the DQoL questionnaire, referring to the satisfaction with the time spent in managing diabetes, was significantly reduced from 2.3 ± 0.8 at baseline to 1.9 ± 0.7 at 3 months (p = 0.001). When asked about their general satisfaction with the system, all the patients expressed a better satisfaction with the system. Some of the comments were as follows: "the system has given me freedom and peacefulness", "I have more independence and autonomy", "it allows a great glycaemic control with the minimum patient intervention", "it learns very fast" and "I have been below 180 mg/dl almost every day". When asked about the things they would like to see improved in the system, some of the answers were "I would like to have different glucose targets for different periods", "I would like to be able to intervene more, to correct when I am going high" and "I would like to be able to bolus from the mobile phone". When asked about the best feature of the system, the most frequent answer was "the auto-correction boluses".

Discussion

The use of automated insulin infusion systems for the management of T1D is rapidly expanding. As more systems are being incorporated into the market, a better understanding of their performance in the clinical setting is even more necessary. An evaluation of patient satisfaction and quality of life is essential to help clinicians better direct their use of diabetes technology. Our study reports the real-world benefit in terms of glycaemic control and of patient satisfaction after 3 months of use of the recently launched Medtronic MiniMed 780G system.

We previously reported the rapid increase in TIR 70-180 mg/dl after the implementation of the 780G system. With the present additional analysis, we confirm that the improvement in TIR 70-180 mg/dl, to an optimal level of > 80%, is sustained after 3 months of use of the system. Previous analyses have shown an increase in TIR 70-180 from 68.8% to 74.5% [22] and from 63% to 67% [23] after 3 months in different populations of adolescents and adults. Also, Collyns *et al*. [24] found a 12.5% increase in TIR 70-180 mg/dl after 1 month of use in children and adults.

Our data provide reassurance that a glucose target of 100 mg/dl and an active insulin time of 2 hours are safe settings and allow the optimisation of the system. Most of the patients benefit from these aggressive settings, although the optimal setting for each patient should be individualised and discussed with the patient. In previous studies, the best outcomes were also obtained with the most aggressive settings [22, 24].

Regarding the use of the system, almost 30% of the bolus insulin was administered as auto-correction boluses, showing that the auto-correction bolus function was extensively used and contributed to the improved outcomes. Additionally, Auto-Mode was used 94% of the time

and only one exit to Manual Mode took place every week. These data agree with previous studies, that show a time in Auto-Mode > 90% and 1.2-1.7 exits per week [22-24].

Beyond glycaemic control, patient satisfaction with the system is crucial to assure long-term use. The previous studies evaluating the psychological impact of closed-loop systems use agree with our data in relation to the high level of general satisfaction expressed by the users and the more flexible lifestyle they experience [10, 13-21]. A high percentage of discontinuation had been reported with the first commercialised HCL system [42]. With this AHCL system, patient satisfaction has been found to be much improved [43].

In our data, a better quality of life has been shown, similarly to the improvement in the quality of life and the general well-being found in other studies [19, 21]. In the same way, an improved quality of sleep with the use of closed-loop system has been shown in several trials [13, 18 19]. When specifically evaluating sleep quality, our results reproduce the results in the Collyns *et al*. analysis, showing a decrease in PSQI, meaning a better sleep quality with the 780G AHCL system [43]. Also, in our subjects, the people with T1D reported an increased satisfaction with the glucose monitoring system. The sensor used at baseline and at the 3-month evaluation was the same, Guardian 3 sensor®, but probably the fact that the system itself chose the optimal glucose values for calibration led to better satisfaction.

The fear of hypoglycaemia has been shown to be reduced in some studies evaluating the patients experiences with artificial pancreas systems [14, 17], but not in others; i.e., Kropff *et al*. found a numerical but not significant reduction in the HFS score [16]. In our group of people with T1D, a significant improvement in HFS was found, due to an improvement in behaviour subscale.

The HFS is the sum of two subscales, worry and behaviour. We only found a significant difference after 3 months of use of the 780G system in the global HFS score and the behaviour subscale score, while the worry subscale score was not statistically different. We interpret this result as the patients taking less actions to avoid hypoglycaemia and its consequences, as they believed the system was being safe, while they still have felt worried about the possibility of having hypoglycaemia episodes in certain situations in the future.

No differences were seen in our patients in the DDS and the DST scores. We could hypothesise that the lack of changes in these scores, in our patients, could reflect a lack of effect of the new system, the 780G, in diabetes distress and diabetes satisfaction with the treatment or it could also be explained by the lack of specificity of these questionnaires to capture the psychological effect of the use of the closed-loop system in the person with type 1 diabetes. However, generally, some differences have to be expected when comparing the results of the psychological evaluation of different closed-loop systems, as they all have their distinct outcomes and requirements from the user. Weissberg-Benchell *et al.* found a reduction in the DDS scores and greater treatment satisfaction with the use of a bihormonal delivery system [17], whilst Kropff *et al*. found no changes in the DST score [16].

The main limitations of the study are that no randomisation was performed and that no control group on SAP-PLGS was included, therefore comparison in the outcomes at the end of follow-up was not possible.

Our study has several strengths including its prospective design, the inclusion of a wide range of ages, from adolescents to older patients and the analysis of clinical and psychological

variables. To the best of our knowledge, this study represents the first assessment of clinical outcomes and psychosocial evaluation after the commercial launch of the Medtronic AHCL 780G system.

In conclusion, in a real-world clinical setting, people with T1D using the AHCL Medtronic 780G system benefit from a sustained improvement in glycaemic outcomes as well as a higher level of user satisfaction.

Declarations

The authors received no funding from an external source.

P.B. has received speaking/consulting honoraria from Medtronic Diabetes, Roche Diabetes, Abbot, Novalab and Lilly. F.A. has received speaking/consulting honoraria from Medtronic Diabetes, Abbot and Lilly. The rest of the authors declare no conflict of interest.

Part of the content of this study has been submitted for its presentation at the 57th EASD annual meeting.

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Table 1. Outcomes in glycaemic control at 3 months compared to baseline.

	Baseline	3 months	p
HbA1c (mmol/mol) (%)	56 ± 10 7.23 ± 0.86	49 ± 7 6.67 ± 0.61	**< 0.001**
Time 70-180 mg/dl (%)	67.3 ± 13.6	80.1 ± 7.5	**< 0.001**
Time > 180 mg/dl (%)	29.4 ± 15.1	16.8 ± 8.4	**< 0.001**
Time > 250 mg/dl (%)	6.9 ± 7.8	2.7 ± 3.0	**< 0.001**
Time < 70 mg/dl (%)	3.4 ± 3.4	3.1 ± 2.5	0.562
Time < 54 mg/dl (%)	0.9 ± 1.2	0.7 ± 0.9	0.127
GMI (%)	6.96 ± 0.53	6.57 ± 0.32	**< 0.001**
Sensor glucose (mg/dl)	155 ± 23	137 ± 13	**< 0.001**
SD (mg/l)	52 ± 10	45 ± 8	**< 0.001**
CV (%)	34 ± 5	33 ± 4	**0.059**
Sensor use (%)	85 ± 11	90 ± 11	**0.001**
Insulin dose (U/day)	44 ± 20	46 ± 21	**0.004**
Insulin dose (U/Kg/day)	0.61 ± 0.23	0.64 ± 0.26	**0.002**
Insulin dose (% of basal insulin)	51 ± 12	43 ± 8	**< 0.001**
Insulin dose (% of bolus insulin)	49 ± 12	57 ± 8	**< 0.001**
Carbohydrate intake (grams per day)	138 ± 75	151 ± 77	0.088
SMBG (number per day)	4.5 ± 1.6	3.6 ± 1.1	**< 0.001**

n = 52. Baseline: sensor-augmented pump with predictive low-glucose suspend function. GMI: glucose management indicator; SD: standard deviation of glucose; CV: coefficient of variation of glucose. Bold meaning significant difference.

Table 2. Parameters reflecting the performance of the AHCL system after 3 months of use.

	Mean ± DS
Time in Auto-Mode (%)	94 ± 10
Exits from Auto-Mode (number of exits per week)	1.0 ± 0.8
SMBG (number per day)	3.6 ± 1.1
Calibrations (number per day)	3.2 ± 1.0
Alarms (number per day)	
hyperglycaemia alarms	1.9 ± 1.8
hypoglycaemia alarms	3.5 ± 3.0
Auto-correction boluses	
number of boluses per day	27 ± 10
units of insulin per day	7 ± 5
percentage of bolus insulin	29 ± 12

n = 52.

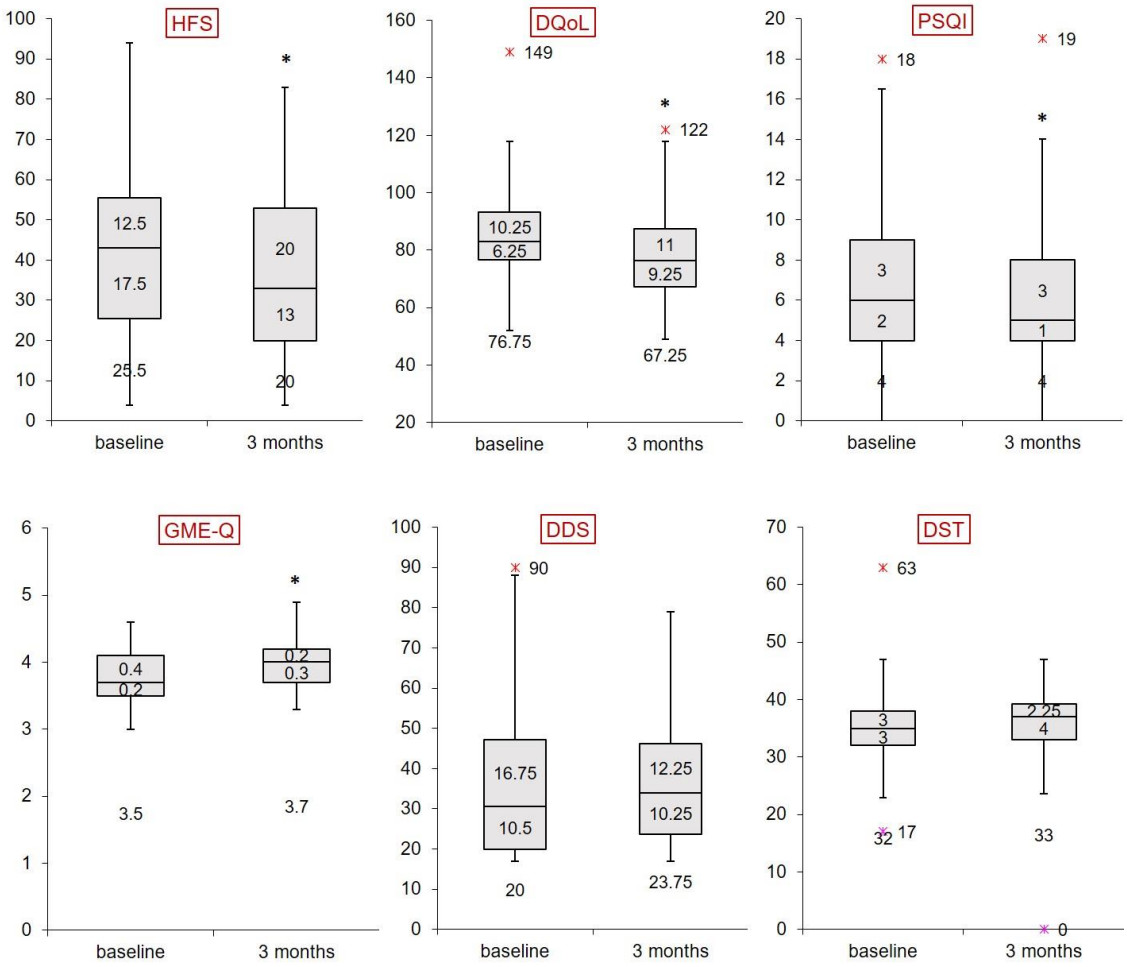

Figure 1. Changes in patient-reported outcomes after 3 months of use of the AHCL system, compared to baseline. Box plots represent median, maximum, minimum and 25th and 75th percentiles for scores in the following questionnaires: Hypoglycaemia Fear Survey, Diabetes Quality of Life, Pittsburgh Sleep Quality Index, Glucose monitoring experience questionnaire, Diabetes Distress Scale and Diabetes Treatment Satisfaction. *$p < 0.005$. HFS (Hypoglycaemia Fear Survey): lower scores indicating less fear of hypoglycemia; DQoL (Diabetes Quality of Life): lower scores indicating a better quality of life; Pittsburgh Sleep Quality Index: lower scores indicating better sleep Quality; GME-Q (Glucose monitoring experience questionnaire): higher scores indicating higher satisfaction with the monitoring system; DDS (Diabetes Distress Scale) and DTS (Diabetes Treatment Satisfaction): no significantly different scores.

Title

Amelioration of user experiences and glycaemic outcomes with an Advanced Hybrid Closed Loop System in a real-world clinical setting.

Running title: Satisfaction with Medtronic MiniMed 780G system

Author

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Abstract

Aims. Automation in diabetes technology is rapidly evolving. The aim was to evaluate the real-world glycemic outcomes and user acceptance after 3 months of using the Medtronic 780G Advanced Hybrid Closed-Loop (AHCL) system.

Methods. A prospective analysis was performed. A glucose target of 100 mg/dl and an active insulin time of 2 hours were set. Capillary HbA1c, 2-week of pump and sensor data and several satisfaction questionnaire scores were compared at baseline and after 3 months of using the AHCL system.

Results. 52 subjects were selected (age: 43±12 years, sex: 73% female, diabetes duration: 27±11 years, higher education: 31%). Time in range (TIR) 70-180 mg/dl increased from 67.3±13.6% to 80.1±7.5% and time >180 mg/dl and >250 mg/dl were reduced (16.8±8.4 *vs* 29.4±15.1%, 2.7±3.0% *vs* 6.9±7.8%, respectively) (all $p<0.001$), while time in hypoglycaemia remained below recommended targets. Time in Auto-Mode and sensor use were 94±10% and 90±11%, respectively. Auto-correction boluses represented 29±12% of bolus insulin. Fear of hypoglycaemia, diabetes quality of life, sleep quality and satisfaction with the monitoring system improved after 3 months.

Conclusion. The real-world use of the AHCL system Medtronic 780G provides an 80.1% TIR 70-180 mg/dl with minimal hypoglycaemia and an increased level of patient satisfaction.

Keywords: type 1 diabetes, advanced hybrid closed loop system, patient satisfaction.

Introduction

The use of different technology options has become the standard of care for the management of people with type 1 diabetes (T1D). Consecutive advances in the automation of the systems have led to a reduction in time in hypoglycaemia and an increase in time in range between 70 mg/dl and 180 mg/dl (TIR 70-180 mg/dl). The low-glucose suspend function was the first automation in sensor-augmented pumps and it was followed by the predictive low-glucose suspend feature (SAP-PLGS) [1].

The latest automated insulin infusion systems, so-called closed-loop systems or artificial pancreas systems, include control algorithms that continuously decide the infusion of insulin according to real-time glucose sensor values. International consensus recommends a 70% TIR 70-180 mg/dl as the target for people with T1D [2, 3] and artificial pancreas were the first systems to allow the majority of patients to reach that 70% target [4]. Also, these systems have been shown to offer the maximum benefit in a real-world setting [5,6].

With the evolution of automation in diabetes technology, improvement in TIR 70—180 mg/dl has been accompanied by a higher level of patient satisfaction [7-11]. In this context, several aspects of the user experience with closed-loop systems are recognised to impact patient-reported outcomes. Maintaining the patient as close as possible to normoglycaemia, by avoiding hyperglycaemia while minimising hypoglycaemia is one of the main goals of automated insulin delivery; consequently, a reduction in fear of hypoglycaemia and an increased feeling of safety are expected after the introduction of a closed-loop system. Also, the glucose sensor is an essential component of closed-loop systems; its accuracy, the number of alerts it generates and

its calibration requirements should have an impact int the overall patient satisfaction with the system. In addition, changes in sleep quality might be expected after the implementation of a closed-loop system; first, the improvement in glycaemic control could reduce the number of nocturnal hyperglycaemia and hypoglycaemia episodes, having a positive impact on sleep quality; on the other hand, the possible alerts generated by the system requirements or malfunctions could harm patient sleep. All these aspects together would probably have a deep impact on the overall quality of life in closed-loop system users. Validated and reliable tools to assess the relevant perceived benefits and burdens in relation to automated insulin delivery systems are being developed [12].

The mentioned psychological impact of the use of closed-loop systems has been previously evaluated in clinical trials [10, 11, 13-21]. Patients' preferences and views regarding the use of closed-loop systems have been assessed through interviews, psychological questionnaires and online surveys in adults, adolescents, children and parents. Overall, the level of satisfaction and acceptance of closed-loop systems has been reported to be high. The main positive remarks refer to less diabetes burden and distress, improved glycaemic control, better sleep quality, improved general well-being and quality of life and reduction in worries about hypoglycaemia and hyperglycaemia. The key negative points expressed by the users are technical difficulties and connectivity issues, discomfort, the intrusiveness of alarms and the devices wearability.

The Advanced Hybrid Closed-Loop (AHCL) system Medtronic MiniMed 780G was launched in Europe in October 2020. This system automatically infuses insulin according to interstitial sensor glucose values, to different glucose targets (100, 110 or 120 mg/dl) and it also delivers

auto-correction boluses to a glucose target of 120 mg/dl. Precommercial studies showed an increase in TIR 70-180 mg/dl from 5.7% to 12.5% in different groups of patients [22-24].

We have previously reported a preliminary analysis showing the rapid improvement in glycaemic control achieved in the first 30 days after the initiation of the 780G system, showing a 12.3% improvement in TIR 70-180 mg/dl from day 1 [25]. The aim of this study was to evaluate the real-world benefits of the Medtronic 780G AHCL system, in terms of glycaemic control and of patient acceptance, after 3 months of use, in the same group of patients.

Material and Methods

A longitudinal prospective protocol was designed. Patients using the SAP-PLGS Medtronic 640G system were simultaneously upgraded to the AHCL Medtronic 780G system. Pregnant patients were not included. The study subjects participated in a training session to start the system in Manual Mode and to explain its functioning. One week later, another training session was scheduled to explain the Auto-Mode and initiate its use. The duration of both training sessions was 3 hours. The bolus calculator settings were programmed equally to the previous configuration. An active insulin time of 2 hours and a glucose target of 100 mg/dl was programmed for all the patients, according to protocol. All the patients had the auto-correction bolus function activated.

At baseline and after 3 months of use of Auto-Mode, several variables were recorded, including weight, height and capillary HbA1c, measured by Afinion^{TM}. Two-week of sensor and

insulin data were downloaded for the system, both the 640G, at baseline and the 780G, at 3 months. The following data were collected from the downloads: TIR 70-180 mg/dl, time < 54 mg/dl and < 70 mg/dl, time > 180 and > 250 mg/dl, sensor use, mean glucose sensor levels, standard deviation of sensor glucose, coefficient of variation of sensor glucose, total daily insulin dose, number of SMBGs per day and sensor use. Variables related to the use of the system at the end of follow-up were also assessed, including time in Auto-Mode, the number of exits from Auto-Mode per week and the reasons for these exits, the amount of insulin given as autocorrection boluses and the number of calibrations.

The subjects were asked to complete, at baseline and at the 3-month visit, the following questionnaires, in their Spanish validated versions: Hypoglycaemia Fear Survey (HFS) to evaluate fear of hypoglycaemia [26-28], Glucose Monitoring Experience Questionnaire (GME-Q) to assess satisfaction with the glucose monitoring system [29, 30], Gold and Clarke scores to analyse hypoglycaemia awareness [31-33], Diabetes Quality of Life (DQoL) for quality of life assessment [34, 35], Diabetes Distress Scale (DDS) to measure diabetes-related stress [36, 37], diabetes satisfaction with the treatment (DST) [38, 39] and Pittsburgh Sleep Quality Index to evaluate sleep quality (PSQI) [40, 41].

In summary, The HFS comprises 33 items, grouped in 2 subscales, behaviour subscale and worry subscale, with 5 possible answers por each question, to sum a global score; higher scores represent increased fear of hypoglycaemia. The GME-Q includes 23 items, with 3 subscales (effectiveness, intrusiveness, convenience), with a 5-point Likert scale; higher scores indicate higher satisfaction with the monitoring system. The Gold score evaluates hypoglycaemia

awareness with a single question about hypoglycaemia awareness, that the patient has to rate from 1 to 7; the Clarke score is formed of 8 questions, with different possible answers; in both cases, a score > 3 reflects impaired awareness of hypoglycaemia. The DQoL questionnaire has 42 questions, grouped in 4 subscales (patient satisfaction, impact generated by diabetes, worry about diabetes and social worry), with 5 possible answers, and higher scores indicate a poorer quality of life. The DDS is formed by 17 items, with a 6-point Likert scale, and higher scores represent higher distress. The DST questionnaire is comprised of 8 items, with a 0 to 6 scale, and higher scores represent higher satisfaction with the diabetes treatment. The PSQI questionnaire includes 19 items, with a 0 to 3 scale; higher scores represent poorer sleep quality; a score > 5 is considered a poor sleep quality.

Also, the following open questions were asked to the patients to assess their general satisfaction with the system: *what is s your opinion on the 780G system? what has been improved in the 780G system, compared to the 640G system? what is worse in the 780G system, compared to the 640G system? has your glycaemic control improved? do you have more hypoglycaemic events? do you find it easier to control your diabetes? do you get more or fewer alerts? do you sleep better or worse? what would you improve in the 780G system?*

The study protocol followed the Declaration of Helsinki principles and was approved by the Badajoz University Hospital Ethics Committee (date: 22 October 2020). All the participants were informed of the protocol and signed a consent form.

Data analysis was performed using the SPSS statistics software v22. Results are presented as mean ± SD values. A paired Student's t-test was used for the analysis of differences. For

unpaired samples, the independent samples t-test was used. A McNemar test was used to compare proportions for paired data. Correlation analyses were performed using the Pearson correlation coefficient. A p-value < 0.05 was considered statistically significant.

Results

52 people with T1DM were included in the study. Demographic characteristics were as follows: age: 43 ± 12 years (15-65), 10% (n = 5) adolescents and young adults (< 21 years old), sex: 73% (n = 38) female, diabetes duration: 27 ± 11 years, BMI: 25 ± 5 kg/m^2, higher education: 31% (n = 16), time on pump: 6.5 ± 3.4 years, time on SAP-PLGS: 4.6 ± 2.2 years.

Glycaemic outcomes.

The outcomes after 3 months of use of the AHCL system, compared to the outcomes at baseline, with the SAP-PLGS system, are summarised in Table 1. An increase of TIR 70-180 mg/dl from 67.3 ± 13.6% to 80.1 ± 7.5% was found (p < 0.001), with a range of TIR 70-180 mg/dl from 59% to 94% at 3 months. Also, HbA1c decreased from 56 ± 10 mmol/mol to 49 ± 7 mmol/mol (7.23 ± 0.86% to 6.67 ± 0.61%) (p < 0.001).

The percentage of patients with HbA1c ≤ 53 mmol/mol (7%) increased from 46% (n = 24) at baseline to 67% (n = 35) at 3 months (p = 0.001). The percentage of patients with TIR 70-180 mg/dl > 70% increased from 46% (n = 24) at baseline to 89% (n = 46) at 3 months (p < 0.001). The 6 patients who did not reach the target of TIR 70-180 mg/dl > 70% had a TIR 70-180 mg/dl of 59%, 65%, 67%, 68% and 70% (2 patients). The percentage of patients with TIR 70-180 mg/dl >

70% and time < 70 mg/dl < 4% increased from 31% (n = 16) at baseline to 60% (n = 31) at 3 months (p = 0.001). No severe hypoglycaemia or diabetic ketoacidosis episodes occurred during follow-up.

Four patients were diagnosed with SARS-CoV-2 infection and were confined for 14 days. Neither of them required hospitalization due to infection severity or to deterioration of glycaemic control, and the system was maintained in Auto-Mode during the infection.

Use of the system.

The parameters reflecting the functioning of the AHCL system after 3 months of use are detailed in Table 2. A significant amount of auto-correction boluses was administered by the system, representing 29 ± 12% of the percentage of bolus insulin, with a wide range (from 10% to 68%). A significant negative correlation was found between TIR 70-180 mg/dl and the percentage of insulin delivered as auto-correction boluses ($r = -0.704$, $p < 0.001$).

When evaluating the system settings at 3 months, 94% (n = 49) of the participants had maintained the glucose target of 100 mg/dl and an active insulin time of 2 hours during the 3 months of study. Two patients had switched their glucose target to 110 mg/dl, due to high hypoglycaemia frequency. An additional patient had increased the glucose target to 110 mg/dl and the active insulin time to 3 hours, due to extreme fear of hypoglycaemia, without actually having experienced hypoglycaemia episodes. All 52 subjects kept the auto-correction function activated. No changes were seen in the grams of carbohydrate to insulin ratios programmed in the system for any of the meals.

The main reason for the system exiting from Auto-Mode to Manual Mode was "SmartGuard deactivated by the user" (31%) followed by "end of sensor life" (19%), "no calibration" (17%) and "sensor update" (16%). The rest of the reasons were uncommon (less than 8%).

The number of hyperglycaemia alarms was reduced from 2.8 ± 3.2 to 1.9 ± 1.8 alarms per day (p = 0.037), while the number of hypoglycaemia alarms increased from 2.5 ± 2.6 to 3.5 ± 3.0 alarms per day (p = 0.007).

Patient-reported outcomes.

The Clarke score was reduced from 2.49 ± 1.9 at baseline to 2.14 ± 2.0 at the 3-month visit (p = 0.04). The Gold score was not significantly reduced (3.5 ± 1.7 at baseline *vs* 3.1 ± 2.0 at the 3-month visit ; p = 0.084). The changes in the scores in the different questionnaires regarding patient-reported outcomes are shown in Figure 1 in box plots, representing median, maximum, minimum and 25^{th} and 75^{th} percentiles. Regarding fear of hypoglycaemia, although HFS score was significantly reduced after 3 months (46 ± 25 at baseline *vs* 37 ± 23 at 3 months, p = 0.002), reflecting a reduction in fear of hypoglycaemia, this difference was due to an improvement in the behaviour subscale (19 ± 11 at baseline *vs* 14 ± 10 at 3 months, p = 0.002), while the changes in the worry subscale were not significant (26 ± 18 at baseline *vs* 22 ± 18 at 3 months, p = 0.072). Diabetes quality of life, evaluated by the DQoL questionnaire, showed a decrease in the score at 3 months, compared to baseline (81 ± 21 at baseline vs 76 ± 16 at 3 months, p = 0.036), meaning better quality of life. The GME-Q score increased, from 3.8 ± 0.4 to 4.0 ± 0.4, p = 0.007, reflecting a better experience with the glucose sensor. Also, a lower PSQI score was seen with the AHCL

system compared to baseline (5.8 ± 3.5 *vs* 6.6 ± 3.8, p = 0.047), reflecting a better sleep quality. No differences were found in the DST or DDS scores.

One patient (male, 25 years old, engineer) decided to stop using the Auto-Mode after 4 days of use, despite a better glycaemic control (85% TIR 70-180 mg/dl *vs* 67% at baseline) as he preferred to be able to manually adjust the insulin infusion, and he was excluded from the analysis. The rest of the patients expressed their desire to continue using the system.

The score in the first question in the DQoL questionnaire, referring to the satisfaction with the time spent in managing diabetes, was significantly reduced from 2.3 ± 0.8 at baseline to 1.9 ± 0.7 at 3 months (p = 0.001). When asked about their general satisfaction with the system, all the patients expressed a better satisfaction with the system. Some of the comments were as follows: "the system has given me freedom and peacefulness", "I have more independence and autonomy", "it allows a great glycaemic control with the minimum patient intervention", "it learns very fast" and "I have been below 180 mg/dl almost every day". When asked about the things they would like to see improved in the system, some of the answers were "I would like to have different glucose targets for different periods", "I would like to be able to intervene more, to correct when I am going high" and "I would like to be able to bolus from the mobile phone". When asked about the best feature of the system, the most frequent answer was "the auto-correction boluses".

Discussion

The use of automated insulin infusion systems for the management of T1D is rapidly expanding. As more systems are being incorporated into the market, a better understanding of their performance in the clinical setting is even more necessary. An evaluation of patient satisfaction and quality of life is essential to help clinicians better direct their use of diabetes technology. Our study reports the real-world benefit in terms of glycaemic control and of patient satisfaction after 3 months of use of the recently launched Medtronic MiniMed 780G system.

We previously reported the rapid increase in TIR 70-180 mg/dl after the implementation of the 780G system. With the present additional analysis, we confirm that the improvement in TIR 70-180 mg/dl, to an optimal level of > 80%, is sustained after 3 months of use of the system. Previous analyses have shown an increase in TIR 70-180 from 68.8% to 74.5% [22] and from 63% to 67% [23] after 3 months in different populations of adolescents and adults. Also, Collyns *et al*. [24] found a 12.5% increase in TIR 70-180 mg/dl after 1 month of use in children and adults.

Our data provide reassurance that a glucose target of 100 mg/dl and an active insulin time of 2 hours are safe settings and allow the optimisation of the system. Most of the patients benefit from these aggressive settings, although the optimal setting for each patient should be individualised and discussed with the patient. In previous studies, the best outcomes were also obtained with the most aggressive settings [22, 24].

Regarding the use of the system, almost 30% of the bolus insulin was administered as auto-correction boluses, showing that the auto-correction bolus function was extensively used and contributed to the improved outcomes. Additionally, Auto-Mode was used 94% of the time

and only one exit to Manual Mode took place every week. These data agree with previous studies, that show a time in Auto-Mode > 90% and 1.2-1.7 exits per week [22-24].

Beyond glycaemic control, patient satisfaction with the system is crucial to assure long-term use. The previous studies evaluating the psychological impact of closed-loop systems use agree with our data in relation to the high level of general satisfaction expressed by the users and the more flexible lifestyle they experience [10, 13-21]. A high percentage of discontinuation had been reported with the first commercialised HCL system [42]. With this AHCL system, patient satisfaction has been found to be much improved [43].

In our data, a better quality of life has been shown, similarly to the improvement in the quality of life and the general well-being found in other studies [19, 21]. In the same way, an improved quality of sleep with the use of closed-loop system has been shown in several trials [13, 18 19]. When specifically evaluating sleep quality, our results reproduce the results in the Collyns *et al*. analysis, showing a decrease in PSQI, meaning a better sleep quality with the 780G AHCL system [43]. Also, in our subjects, the people with T1D reported an increased satisfaction with the glucose monitoring system. The sensor used at baseline and at the 3-month evaluation was the same, Guardian 3 sensor®, but probably the fact that the system itself chose the optimal glucose values for calibration led to better satisfaction.

The fear of hypoglycaemia has been shown to be reduced in some studies evaluating the patients experiences with artificial pancreas systems [14, 17], but not in others; i.e., Kropff *et al*. found a numerical but not significant reduction in the HFS score [16]. In our group of people with T1D, a significant improvement in HFS was found, due to an improvement in behaviour subscale.

The HFS is the sum of two subscales, worry and behaviour. We only found a significant difference after 3 months of use of the 780G system in the global HFS score and the behaviour subscale score, while the worry subscale score was not statistically different. We interpret this result as the patients taking less actions to avoid hypoglycaemia and its consequences, as they believed the system was being safe, while they still have felt worried about the possibility of having hypoglycaemia episodes in certain situations in the future.

No differences were seen in our patients in the DDS and the DST scores. We could hypothesise that the lack of changes in these scores, in our patients, could reflect a lack of effect of the new system, the 780G, in diabetes distress and diabetes satisfaction with the treatment or it could also be explained by the lack of specificity of these questionnaires to capture the psychological effect of the use of the closed-loop system in the person with type 1 diabetes. However, generally, some differences have to be expected when comparing the results of the psychological evaluation of different closed-loop systems, as they all have their distinct outcomes and requirements from the user. Weissberg-Benchell *et al.* found a reduction in the DDS scores and greater treatment satisfaction with the use of a bihormonal delivery system [17], whilst Kropff *et al*. found no changes in the DST score [16].

The main limitations of the study are that no randomisation was performed and that no control group on SAP-PLGS was included, therefore comparison in the outcomes at the end of follow-up was not possible.

Our study has several strengths including its prospective design, the inclusion of a wide range of ages, from adolescents to older patients and the analysis of clinical and psychological

variables. To the best of our knowledge, this study represents the first assessment of clinical outcomes and psychosocial evaluation after the commercial launch of the Medtronic AHCL 780G system.

In conclusion, in a real-world clinical setting, people with T1D using the AHCL Medtronic 780G system benefit from a sustained improvement in glycaemic outcomes as well as a higher level of user satisfaction.

Declarations

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P.B. has received speaking/consulting honoraria from Medtronic Diabetes, Roche Diabetes, Abbot, Novalab and Lilly. F.A. has received speaking/consulting honoraria from Medtronic Diabetes, Abbot and Lilly. The rest of the authors declare no conflict of interest.

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Table 1. Outcomes in glycaemic control at 3 months compared to baseline.

	Baseline	3 months	p
HbA1c (mmol/mol) (%)	56 ± 10 7.23 ± 0.86	49 ± 7 6.67 ± 0.61	**< 0.001**
Time 70-180 mg/dl (%)	67.3 ± 13.6	80.1 ± 7.5	**< 0.001**
Time > 180 mg/dl (%)	29.4 ± 15.1	16.8 ± 8.4	**< 0.001**
Time > 250 mg/dl (%)	6.9 ± 7.8	2.7 ± 3.0	**< 0.001**
Time < 70 mg/dl (%)	3.4 ± 3.4	3.1 ± 2.5	0.562
Time < 54 mg/dl (%)	0.9 ± 1.2	0.7 ± 0.9	0.127
GMI (%)	6.96 ± 0.53	6.57 ± 0.32	**< 0.001**
Sensor glucose (mg/dl)	155 ± 23	137 ± 13	**< 0.001**
SD (mg/l)	52 ± 10	45 ± 8	**< 0.001**
CV (%)	34 ± 5	33 ± 4	**0.059**
Sensor use (%)	85 ± 11	90 ± 11	**0.001**
Insulin dose (U/day)	44 ± 20	46 ± 21	**0.004**
Insulin dose (U/Kg/day)	0.61 ± 0.23	0.64 ± 0.26	**0.002**
Insulin dose (% of basal insulin)	51 ± 12	43 ± 8	**< 0.001**
Insulin dose (% of bolus insulin)	49 ± 12	57 ± 8	**< 0.001**
Carbohydrate intake (grams per day)	138 ± 75	151 ± 77	0.088
SMBG (number per day)	4.5 ± 1.6	3.6 ± 1.1	**< 0.001**

n = 52. Baseline: sensor-augmented pump with predictive low-glucose suspend function. GMI: glucose management indicator; SD: standard deviation of glucose; CV: coefficient of variation of glucose. Bold meaning significant difference.

Table 2. Parameters reflecting the performance of the AHCL system after 3 months of use.

	Mean ± DS
Time in Auto-Mode (%)	94 ± 10
Exits from Auto-Mode (number of exits per week)	1.0 ± 0.8
SMBG (number per day)	3.6 ± 1.1
Calibrations (number per day)	3.2 ± 1.0
Alarms (number per day)	
hyperglycaemia alarms	1.9 ± 1.8
hypoglycaemia alarms	3.5 ± 3.0
Auto-correction boluses	
number of boluses per day	27 ± 10
units of insulin per day	7 ± 5
percentage of bolus insulin	29 ± 12

n = 52.

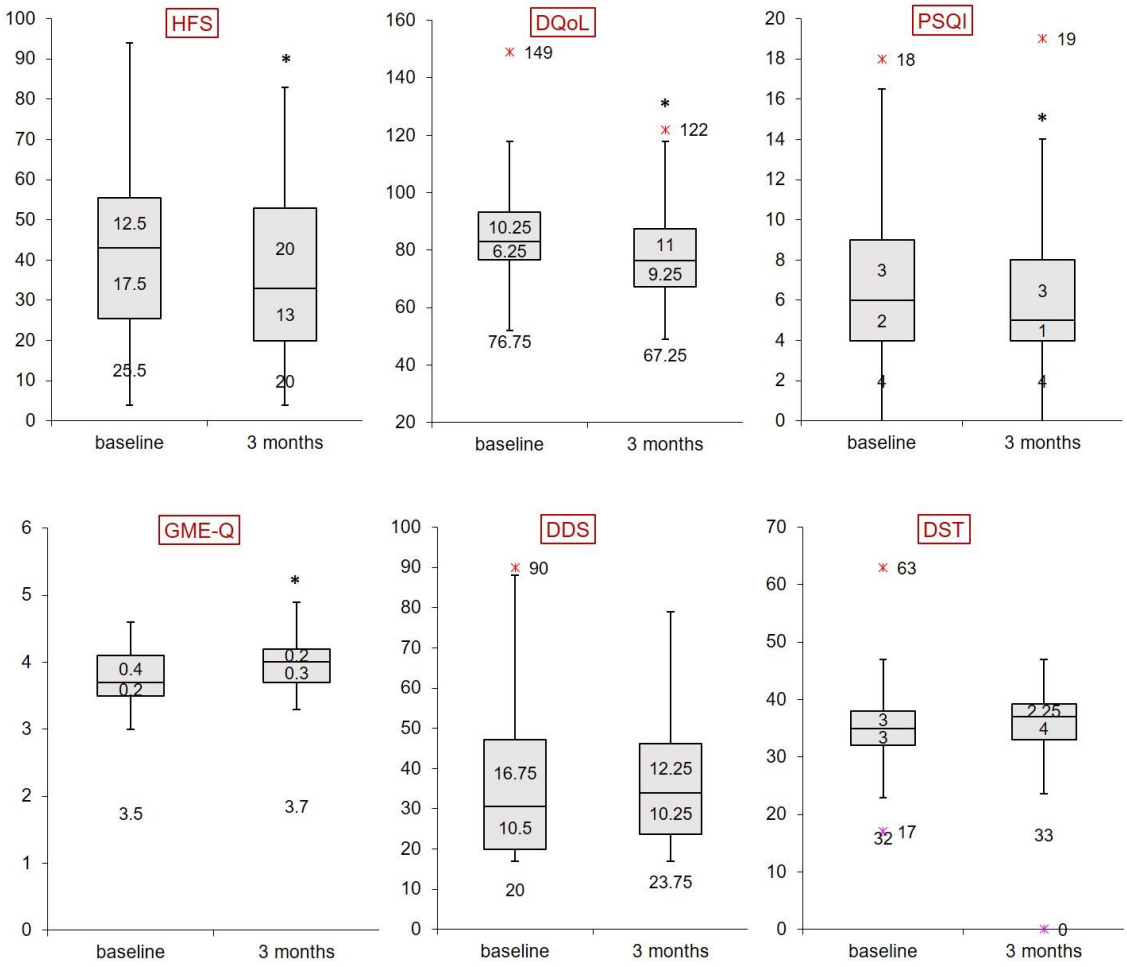

Figure 1. Changes in patient-reported outcomes after 3 months of use of the AHCL system, compared to baseline. Box plots represent median, maximum, minimum and 25th and 75th percentiles for scores in the following questionnaires: Hypoglycaemia Fear Survey, Diabetes Quality of Life, Pittsburgh Sleep Quality Index, Glucose monitoring experience questionnaire, Diabetes Distress Scale and Diabetes Treatment Satisfaction. *$p < 0.005$. HFS (Hypoglycaemia Fear Survey): lower scores indicating less fear of hypoglycemia; DQoL (Diabetes Quality of Life): lower scores indicating a better quality of life; Pittsburgh Sleep Quality Index: lower scores indicating better sleep Quality; GME-Q (Glucose monitoring experience questionnaire): higher scores indicating higher satisfaction with the monitoring system; DDS (Diabetes Distress Scale) and DTS (Diabetes Treatment Satisfaction): no significantly different scores.