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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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ORIGINAL ARTICLE

Observational Study

Evaluation of hybrid closed-loop insulin delivery system in type 1 diabetes in real-world clinical practice: One-year observational study

Ahmed Eldib, Shilton Dhaver, Karim Kibaa, Astrid Atakov-Castillo, Tareq Salah, Marwa Al-Badri, Abdelrahman Khater, Ryan McCarragher, Omnia Elenani, Elena Toschi, Osama Hamdy

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Abstract

BACKGROUND

In 2016, the Food and Drug Administration approved the first hybrid closed-loop (HCL) insulin delivery system for adults with type 1 diabetes (T1D). There is limited information on the impact of using HCL systems on patient-reported outcomes (PROs) in patients with T1D in real-world clinical practice. In this independent study, we evaluated glycemic parameters and PROs over one year of continuous use of Medtronic's 670G HCL in real-world clinical practice.

AIM

To assess the effects of hybrid closed loop system on glycemic control and quality of life in adults with T1D.

METHODS

We evaluated 71 patients with T1D (mean age: 45.5 ± 12.1 years; 59% females; body weight: 83.8 ± 18.7 kg, body mass index: 28.7 ± 5.6 kg/m^2, A1C: 7.6% ± 0.8%) who were treated with HCL at Joslin Clinic from 2017 to 2019. We measured A1C and percent of glucose time-in-range (%TIR) at baseline and 12 months. We measured percent time in auto mode (%TiAM) for the last two weeks preceding the final visit and assessed PROs through several validated quality-of-life surveys related to general health and diabetes management.

RESULTS

At 12 mo, A1C decreased by 0.3% ± 0.1% (P = 0.001) and %TIR increased by 8.1%

± 2.5% (P = 0.002). The average %TiAM was only 64.3% ± 32.8% and was not associated with A1C, %TIR or PROs. PROs, provided at baseline and at the end of the study, showed that the physical functioning submodule of 36Item Short-Form Health Survey increased significantly by 22.9% (P < 0.001). Hypoglycemia fear survey/worry scale decreased significantly by 24.9% (P < 0.000); Problem Areas In Diabetes reduced significantly by -17.2% (P = 0.002). The emotional burden submodules of dietary diversity score reduced significantly by -44.7% (P = 0.001). Furthermore, analysis of Clarke questionnaire showed no increase in awareness of hypoglycemic episodes. WHO-5 showed no improvements in subject's wellbeing among participants after starting the 670G HCL system. Finally, analysis of Pittsburgh Sleep Quality Index showed no difference in sleep quality, sleep latency, or duration of sleep from baseline to 12 mo.

CONCLUSION

The use of HCL in real-world clinical practice for one year was associated with significant improvements in A1C, %TIR, physical functioning, hypoglycemia fear, emotional distress, and emotional burden related to diabetes management. However, these changes were not associated with time in auto mode.

Key Words: Artificial pancreas; Continuous blood glucose monitor; Type 1 diabetes; Hybrid closed-loop insulin delivery; Quality of life

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Core Tip: There has been a growing emphasis on patient-centered healthcare and there are limited data on the impact of hybrid-closed-loop systems on quality-of-life measures. In this study, we aimed to evaluate the glycemic control and quality of life measures in patients with type 1 diabetes in a real-world clinical practice who used hybrid closed loop systems showed improvements in A1C, percent time in optimal glucose range, emotional burden and distress due to diabetes, physical functioning, and fear of hypoglycemia.

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INTRODUCTION

Type 1 diabetes (T1D) affects around 1.6 million patients in the United States[1]. Despite many innovations in T1D management, reaching and maintaining optimal glycemic control remains difficult. The perpetual challenge of self-management and self-monitoring imposed by T1D are significant and put an enormous burden on patients. Moreover, discrepancies between food intake and insulin doses can result in severe and life-threatening acute complications (*e.g.*, severe hyperglycemia or severe hypoglycemia), along with the devastating long-term complications of uncontrolled diabetes, such as obesity, diabetic retinopathy, chronic kidney disease, non-alcoholic fatty liver disease, and cardiovascular disease[2-4]. These challenges call for more practical solutions, including the utilization of diabetes management technology[5]. Insulin pumps, used independently, or in combination with continuous glucose monitors (CGM), have been associated with better glycemic control and lower A1C[6-8]. The introduction of hybrid closed-loop (HCL) systems was a revolutionary step toward better glycemic control. These devices lessen the burden of diabetes self-management by adjusting insulin delivery based on real-time interstitial glucose values. Understanding patients' expectations from these devices is critical to ensure enhanced patient compliance and satisfaction[9,10].

Medtronic's MiniMed 670G (670G) was the first Food and Drug Administration-approved HCL insulin delivery system for patients with T1D[11]. It was followed by 3 other systems, MiniMed's 780G, Tandem's t:slim Control IQ and Insulet's Omnipod 5. In Auto Mode, the integrated CGM captures interstitial glucose values every five minutes, and *via* a built-in algorithm, it automatically adjusts basal insulin delivery, aiming at keeping glucose value around 120 mg/dL. During exercise, the algorithm adjusts glucose target to around 150 mg/dL. Meanwhile, pre-set basal insulin can be delivered throughout the day in manual mode[11,12].

Patients with T1D, who use HCL insulin delivery systems, have better glucose control and decreased risk of hypoglycemia, compared to those using independent sensor-augmented insulin pumps and a CGM[13]. The safety of HCL systems was demonstrated during in-home use by adolescents and adults. The results showed significant A1C reduction, higher percent of glucose time-in-range (%TIR), and lower percentage time in hyperglycemia or hypoglycemia compared to baseline[14,15].

However, data on the impact of HCL systems on quality-of-life measures are limited. Knowledge and understanding of this information are of particular importance due to growing emphasis on patient-centered healthcare. In this

independent prospective observational study, we evaluated clinical and patientreported outcomes (PROs) among patients with T1D who used 670G HCL system in real-world clinical practice over one year.

MATERIALS AND METHODS

Patients and methods

This study was approved by the Committee on Human Studies at the Joslin Diabetes Center. Each participant signed the study informed consent before enrollment in the 12-month observational study period.

We recruited 114 adult patients with T1D who started 670G HCL system at the Joslin Diabetes Adult Clinic between December 2017 and December 2019. Data were collected at baseline and after 12 months. We assessed PROs by administering the following surveys: 36Item Short-Form Health Survey (SF36)[16], Pittsburgh Sleep Quality Index (PSQI)[17], hypoglycemia fear survey/worry scale (HFS_W)[18], Problem Areas In Diabetes (PAID)[19], Well-Being Index (WHO-5)[20], Clarke hypoglycemia awareness survey and Diabetes Distress Scale with its sub sections: Emotional Burden, Physician-related Distress, Regimen-related Distress and Interpersonal Distress[21].

We measured A1C and %TIR at baseline and after 12 months of continuous use. We also evaluated percent time in auto mode (%TiAM) during the two weeks preceding the final study visit.

Out of the 114 participants in the study, 71 patients completed the 12-month follow-up and were included in this final analysis.

Statistical analysis

Demographic and baseline characteristics were expressed as mean ± SD or as mean (95% confidence interval). Categorical variables were expressed as percentages. Chi-square test and paired t-test were used to compare endpoints between baseline and at 12 mo. A P value of < 0.05 was considered statistically significant. All analyses were performed using STATA Special Edition 15.0 for Windows® (StataCorp®, College Station, Texas, United States, 2017).

RESULTS

In this study, we evaluated 71 patients with T1D (mean age: 45.5 ± 12.1 years' 59% females' body weight: 83.8 ± 18.7 kg, body mass index: 28.7 ± 5.6 kg/m^2, A1C: 7.6 ± 0.8%; Table 1).

At 12 mo, A1C decreased by 0.3% ± 0.1% (P = 0.001) and %TIR increased by 8.1% ± 2.5% (P = 0.002; Table 2). The average %TiAM was only 64.3% ± 32.8% and was not associated with A1C, %TIR or PROs at both, the beginning and end of the study.

PROs, provided at baseline and at the end of the study, showed that the physical functioning submodule of SF-36 increased significantly by 22.9% (P < 0.001), with no significant differences observed in other submodules of SF-36. HFS_W decreased significantly by 24.9% (P < 0.001); PAID reduced significantly by -17.2% (P = 0.002); Overall, total dietary diversity score (DDS) was not reduced significantly, but emotional burden submodules of DDS reduced significantly by -44.7% (P < 0.001). Furthermore, analysis of Clarke questionnaire showed no increase in awareness of hypoglycemic episodes. WHO-5 showed no improvements in subject's wellbeing among participants after starting the 670G HCL system. Finally, analysis of PSQI showed no difference in sleep quality, sleep latency, or duration of sleep from baseline to 12 months.

DISCUSSION

In this study, we prospectively followed 71 patients with T1D who started HCL insulin delivery system (Medtronic's MiniMed 670G) for 12 mo in real-world clinical practice. The study showed that glycemic parameters improved significantly where A1C decreased by 0.3% ± 0.1% (P < 0.001), and glucose %TIR increased by 8.1% ± 2.5% (P = 0.002). The improvement in glycemic parameters were associated with improvement in some PROs, including PAID, HFS_W, emotional burden and interpersonal distress submodules of DDS-significant increase in the SF-36 physical functioning score. However, neither of these changes were associated with the %TiAM, which was only 64.3% ± 32.8% of the time wearing the HCL system. The study also showed no improvement in subjects' wellbeing and no difference in sleep quality, sleep latency, or duration of sleep from baseline to 12 months.

The improvement in glycemic parameters in real-world clinical practice are aligned with previous observation on the 670G HCL system in clinical research studies[15,22,23]. In a pivotal MiniMed 670G clinical study, the reduction in A1C ranged from 0.5% to 0.7%[24]. Here, we showed a smaller decrease in A1C of 0.3%. A potential explanation for this difference could be related to the discrepancy in the %TiAM, which was 87% in the pivotal study, in comparison to 64.3% ± 32.8% in this study. Although this could be a logical explanation for the discrepancy in glycemic improvement, our study showed no relationship between glycemic parameters and %TiAM. We could postulate that sensor fatigue and suboptimal follow up in real-world clinical practice played some role. Patients enrolled in clinical trials are generally under close-monitoring and are provided with better support.

Table 1 Baseline characteristics of patients

Variable	Whole cohort (*n* = 71)
Female, *n* (%)	42 (59)
Age (yr)	45.5 ± 12.1
Weight (kg)	83.8 ± 18.7
BMI (kg/m²)	28.7 ± 5.6
Diabetes duration (yr)	30.0 ± 12.7
HbA1c (%)	7.6 ± 0.8

Data are mean ± SD or *n* (%).

Table 2 Changes to glycemic and quality of life parameters after 12 months of using Hybrid-Closed-loop system

	% change from baseline	*P* value[1]
Glycemic parameters (%)		
HbA1c	-0.3	0.001
Time in range	+8.1	0.002
Participant reported outcomes		
SF 36		
Physical functioning	+22.9	< 0.001
Role functioning/physical	-6.3	0.2
Role functioning/emotional	-1.2	0.8
Energy/Fatigue	+1.4	0.6
Emotional well-being	-0.2	0.9
Social functioning	-1.0	0.6
Pain	-1.4	0.6
General health	-0.9	0.7
DDS	-5.6	0.1
Emotional Burden	-44.7	< 0.001
Physician-related Distress	-5.9	0.7
Regimen-related Distress	-5.0	0.2
Interpersonal Distress	-10.5	0.1
PSQI	-1.6	0.8
HFS-W	-24.9	< 0.001
Clarke Hypoglycemia Awareness Survey	+9.5	0.2
WHO-5 Well-Being Index	-5.6	0.2
PAID	-17.2	0.002

[1]Paired *t*-test.
Data are mean percentage change from baseline.
SF36: Short Form-36; DDS: Diabetes Distress Scale; PSQI: Sleep Quality Assessment; HFS-W: Hypoglycemic Fear Survey, Worry subscale; PAID: Problem Areas in Diabetes.

Before this study, there were limited data on the impact of HCL on PROs. Therefore, this study may be of particular importance, since it evaluated significant number of quality-of-life parameters. It is known that the psychological and behavioral aspects of patients who have T1D for long duration significantly influence user adaptation to new diabetes technology. Interestingly, our study showed contradicting results with previous studies[25,26]. McAuley et.al. assessed HCL against usual care in adults with T1D[25]. Their study showed that people on HCL had better diabetes-specific well-being and quality of life without a change in either diabetes distress or treatment satisfaction, which might be explained by the burden of adopting new technologies[25]. Wheeler *et al*[26] conducted a randomized crossover trial, in which they assessed sleep quality and technology satisfaction with using HCL compared to sensor Augmented Pump therapy with Predictive Low Glucose Management in people with T1D. Their study showed a statistically significant improvement in quality of sleep and treatment satisfaction. However, the general psychological health and the worry associated with hypoglycemia persisted. On the contrary, our study showed no significant differences in sleep quality, sleep latency and duration in PSQI. We were expecting an improvement in sleep quality due to reduced episodes and/or alarms for hypoglycemia and decreased requirements for checking blood glucose when patients are symptomatic. In fact, the increased frequency of CGM alarms to calibrate in-order to put the HCL system back into Auto Mode, could be the main reason for lack of improvement in sleep quality.

This study had several limitations. The study lacks social diversity, as it was conducted in a single, tertiary-care center, where majority of participants are well-educated. This might have had an impact on the patients' adoption of new technologies, which might not reflect the same conditions in the general population. Several studies have shown the benefit of technological advancements; such as pumps, devices, and virtual interventions on diabetes management, but also report patients' adoption of technologies as a potential limitation[27,28]. PROs were paper-based, which was convenient for patients to complete and minimized technological barriers but was subject to human errors when transferred electronically from paper forms. Nevertheless, a recent meta-analysis evaluating bias in mode of administering PROs found no bias between paper-based and electronic-based methods[29]. Another limitation is that training patients on PROs was briefly addressed during study initiation. This might have contributed to inconsistency and confusion surrounding some of the provided questionnaires. Also, the lack of a run-in period for device training and incomplete information about participants' history of CGM use further limited this study. Considering that HCL is a newer technology, it comes with the usual burden of participants' adoption and adaptation, which may vary significantly between patients. Furthermore, future research should focus on collecting PROs from a larger sample size, while implementing ample training opportunities to ease the burden of adapting newer technologies. Similar studies are required to evaluate PROs for newer HCL systems; Omnipod 5 and t:slim Control IQ since these HCL systems include a CGM that does not require calibration and could achieve greater %TiAM and possibly improve sleep quality. Another limitation is the lack of data on the type and delivery method of insulin prior to starting the study, as such data could interfere with the outcomes of the study or the effect of the HCL. This independent study from a specialized diabetes center may help industry to improve diabetes technology used for insulin delivery.

CONCLUSION

the use of HCL insulin delivery system in real-world clinical practice results in significant improvements in A1C. This study showed considerable improvements in physical functioning, emotional functioning, and emotional adjustment to various aspects of diabetes management compared to baseline. It also showed that fear of diabetes management over time and the feeling of inappropriate support from family and friends were significantly less. Meanwhile, it showed that the use of HCL is also associated with reduction in fear of hypoglycemic episodes but with no increase in awareness of hypoglycemic episodes. Despite improvement in many PROs, participants' subjective sense of well-being did not show any improvement after starting HCL.

ARTICLE HIGHLIGHTS

Research background

Technology has been playing an increasing role in the management of diabetes. The introduction of hybrid closed-loop (HCL) systems and continuous glucose monitors (CGM) was a revolutionary step toward better glycemic control. However, there is limited data on the impact of HCL on patient-reported outcomes (PROs).

Research motivation

Data on the impact of HCL systems on quality-of-life measures are limited. Knowledge and understanding of this information are of particular importance due to growing emphasis on patient-centered healthcare. This study from a specialized diabetes center may help future research to improve diabetes technology used for insulin delivery.

Research objectives

In this independent prospective observational study, we evaluated clinical and PROs among patients with T1D who used HCL system in real-world clinical practice over one year.

Research methods
Participants with T1D who were treated with HCL at Joslin Clinic from 2017 to 2019 were evaluated. We measured A1C and percent of glucose time-in-range (%TIR) at baseline and 12 months. We measured percent time in auto mode or the last two weeks preceding the final visit and assessed PROs through several validated quality-of-life surveys related to general health and diabetes management.

Research results
At 12 months, A1C decreased by 0.3% ± 0.1% and %TIR increased by 8.1% ± 2.5%. The physical functioning submodule of 36Item Short-Form Health Survey increased significantly by 22.9%. Hypoglycemia fear survey/worry scale decreased significantly by 24.9%; Problem Areas In Diabetes reduced significantly by -17.2%. The emotional burden submodules of dietary diversity score reduced significantly by -44.7%.

Research conclusions
The implementation of HCL in care of T1D in real-world clinical practice for one year is associated with significant improvements in A1C, %TIR, physical functioning, hypoglycemia fear, emotional distress, and emotional burden related to diabetes management.

Research perspectives
Future research should focus on better understanding the effects of HCL system on the patients with diabetes. Larger cohorts are needed for the validation of these results and clinical care should take these outcomes into considerations when deciding on appropriate management for patients.

FOOTNOTES

Author contributions: Eldib A, Dhaver S, Kibaa K and Hamdy O have full access to all study data and take responsibility for data integrity and accuracy of data analysis; Eldib A designed the study, collected data, conducted the statistical analysis, and prepared the manuscript; Dhaver S and Kibaa K collected data, conducted the statistical analysis, and prepared the manuscript; Atakov-Castillo A collected data and reviewed the manuscript; Al-Badri M, Salah T, Khater A, McCarragher R, Elenani O prepared, reviewed, and edited the manuscript; Toschi E and Hamdy O designed and supervised the study, reviewed, and edited the manuscript; all authors approved the final version of the manuscript.

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