CASE REPORT

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The effect of advanced hybrid closed loop system on glycated hemoglobin (HbA1c) in a young male with type 1 diabetes mellitus and growth hormone treatment: A case report

Goran Petrovski [ORCID] | **Fawziya Al Khalaf** | **Judith Campbell** | **Khalid Hussain** | **Emma Day** | **Maheen Pasha**

Division of Endocrinology and Diabetes, Department of Pediatric Medicine, Sidra Medicine, Doha, Qatar

Correspondence
Goran Petrovski, Sidra Medicine, HB 6E 219 PO Box 26999, Al Luqta Street, Education City North Campus, Doha, Qatar.
Email: goran.endo@gmail.com

Abstract
The advanced hybrid closed loop system MiniMed 780G can be an effective tool to improve glycemic control and decrease the health burden in a young male with type 1 diabetes and short stature.

KEYWORDS
advanced hybrid closed-loop system, growth hormone deficiency, growth hormone treatment, type 1 diabetes

1 | INTRODUCTION

A 16-year-old male patient with type 1 diabetes (T1D) and growth hormone (GH) treatment was commenced on the advanced hybrid closed loop (AHCL), MiniMed 780G. His HbA1c decreased from 8.6% to 6.7%, three months after AHCL initiation. AHCL improves glycemic control in T1D patients and is on GH treatment.

Type 1 diabetes (T1D) and growth hormone (GH) deficiency are relatively uncommon. The prevalence of GH deficiency ranges between 1:3500 and 1:8700 with an incidence of T1D below 15 years of age of 1:5000.[1] Combined GH treatment with insulin therapy is rarely prescribed in children and adolescents, and physicians can be reluctant prescribing GH due to deterioration in glycemic control. GH plays an important role in glucose, lipid, and protein metabolism, and its deficiency or excess can impact carbohydrate metabolism.

Initiation of GH treatment in patients with T1D is a challenge for both patients and healthcare providers. Patients need to monitor glucose levels more frequently and adjust insulin doses accordingly, especially at the beginning of GH treatment, while health providers must address specific guidelines for fine-tuning of both basal and bolus insulin.

Glycemic control during the GH treatment can be managed with adequate insulin adjustments, where HbA1c can either remain unchanged[2] or can increase.[3] Continuous subcutaneous insulin infusion (CSII), known as "open loop," can be a preferred method compared to multiple daily injections (MDI), allowing improved management of the nocturnal hyperglycemia caused by insulin resistance consequent to the GH administration.[2]

One of the recent technological advances in diabetes is the integration of CSII with continuous glucose monitoring (CGM) into a closed loop system, such as

advanced hybrid closed loop (HCL) system, MiniMed 780G (Medtronic, Northridge, USA). This novel device, commercially available in Europe (October 2020), uses an algorithm which automatically adjusts the basal insulin delivery every five minutes, in addition with providing automatic bolus insulin correction for high glucose levels, as required. This system potentially gives an opportunity for wider application of managing euglycemia in more difficult situations like combined growth hormone and insulin therapy.

To date, there are no specific reports or guidelines addressing the use of the HCL insulin pump systems during GH treatment in patients with T1D. We therefore present the first report of the advanced HCL system MiniMed 780G insulin pump (Medtronic, Northridge, CA, USA) and demonstrate its effect on HbA1c in an adolescent patient with T1D and GH treatment.

2 | CASE PRESENTATION

This patient was diagnosed with T1D at the age of 13 years. He presented with diabetic ketoacidosis (DKA), plasma glucose 280 mg/dl (70–100 mg/dl), pH 7.2 (7.35–7.45), bicarbonate level 16 mEq/L (21–28 mEq/L), low C-peptide level (0.25 ng/ml (0.78–1.89 ng/ml), positive T1D antibodies (Anti GAD65 0.45 nmol/L (negative values),

Insulin Ab 0.20 nmol/L (negative values), HbA1c of 12.1% (<5.6%), and height for age was −1.5 standard deviation score (SDS) for the predicted mid-parental height. There was no family history of type 1 diabetes mellitus or short stature.

Diabetes education on carbohydrate counting, insulin injections, sick day management, exercise, and treatment of hypoglycemia and hyperglycemia were provided to the family at diagnosis. Personal CGM (Dexcom G5) with individualized alerts (low alert 70 mg/dl, low repeat 15 min, high alert 220 mg/dl, and high repeat 2 h) and multiple daily injections (MDI) of insulin therapy at 0.6 u/kg (basal insulin 16 units and insulin carbohydrate ratio (ICR) 12gr, correction factor (CF) 60 mg/dl, glucose target 120 mg/dl) were also initiated. HbA1c decreased to 8.3% (67 mmol/mol) in the first three months and then to 7.6% (60 mmol/mol) after one year of T1D diagnosis. Satisfactory glycemic control (Table 1) was maintained during this period, with slight increase of insulin dose (0.8 u/kg). The growth velocity (3.8 cm/y) was below the expected for patient's age (>4 cm/y). The patient had regular clinic visits every 3 months with evaluation of insulin therapy, diabetes re-education as needed, and evaluation of the growth velocity.

His growth records revealed consistent delay in height velocity over one year along from −1.5 to −2.4 SDS. Tanner stage II for pubertal staging (testicular volume 4mls

Period	Baseline	A	B	C
Condition	/	T1D	T1D+GHD	T1D+GHD
Treatment	/	MDI	MDI+GHT	AHCL+GHT
Age of presentation, years	/	13.6	15.1	16.2
Duration of treatment, months		15	12	3
Diabetes Data				
HbA1c*, %	12.1	7.7±2.1	9.6±2.8	6.7
HbA1c*, mmol/mol	109	61±23	81±31	50
GMI**, %	/	7.3	8.8	6.4
Insulin, U/kg	0.6	0.8	1.1	1.2
Growth Data				
GH treatment, mg/kg/wk	/	/	0.20	0.22
Height SDS***	−1.5	−2.4	−1.7	−1.2
Growth (height) velocity, cm/y	4.2	3.8	6.2	7.3
Weight, kg	37.5	44.8	72.4	77.2
Weight for age, percentile	16.4	18.2	76.4	85.1

TABLE 1 Diabetes and growth data in the participant before and during GH treatment

Note: Baseline shows the data at the time of T1D diagnosis. * HbA1c is presented as average ±SD for selected period, except on AHCL +GHT. ** GMI presents 3 months data at the end of each treatment period: MDI, MDI+GHT, and AHCL+GHT. *** A Child's Target Height Based on Mid-parental height is −0.61 SDS.

Abbreviations: AHCL, advanced hybrid closed loop; GH, growth hormone; GHD, growth hormone deficiency; GHT, growth hormone treatment; GMI, Glucose Management Index; MDI, multiple daily injections; SDS, standard deviation score; T1D, type 1 diabetes.

bilaterally with a few pubic hair) was noted. Due to the delay in growth velocity, the patient was evaluated for possible GH deficiency. The GH provocation test (Clonidine test) showed a peak GH of 1.1mU/L (>5 mU/L) with low serum IGF-1 level of 5.3 nmol/L thus confirming GH deficiency/insufficiency.[4] GH treatment with Norditropin (somatropin injections, NovoNordisk A/S, Bagsvaerd, Denmark) of 0.20 mg/kg/week was initiated along with diabetes management on fine-tuning of basal insulin and correction dose. Patient's growth improved with GH treatment (height for age −2.4 to −1.7 SDS and growth velocity of 6.2 cm/y) in the first year (Table 1). Despite the increase of insulin dose (0.8–1.1 μ/kg) and close monitoring with personal CGM, the glycemic control deteriorated in the following 12 months (at age of 16 years), where HbA1c increased by almost 2% (Table 1) and glucose time in range (TIR) decreased by 30% during the GH treatment (Figure 1).

An advanced HCL system, MiniMed 780G insulin pump (Medtronic, Northridge, CA, USA), was offered to the family, which was accepted. The primary objective for initiation of advanced HCL was to improve the glycemic control and decrease patient's health burden. The patient and his family were initially anxious regarding the responsibilities of pump therapy, however, were motivated to start, hoping the new treatment would improve glycemic control and reduce the daily burden of both the diabetes and GH deficiency.

The pump introduction (system's expectations and individual's responsibilities) and carbohydrate counting assessment was performed at a clinic visit, once successfully completed the patient was scheduled for regular pump training. The program included four sessions of two hours on four consecutive days: (I) pump buttons and menus, understanding CGM graph, education in sensor calibration and sensor insertion; (II) Manual Mode, bolus wizard use, basal rates, and Carelink mobile apps; (III) SmartGuard Auto Mode and readiness, infusion set, and reservoir change; (IV) hypoglycemia, hyperglycemia, exercise, travel, sick day management, and evaluation to initiate advanced HCL system. Patient's pump knowledge and competency evaluation was assessed as satisfactory to initiate advanced HCL system.

Patient used the advanced HCL in manual mode without reduction in total daily dose (TDD) from MDI for four days, and then, SmartGuard Auto Mode was initiated. Patient's pump and sensor data were synchronized automatically to Carelink Personal Account using the MiniMed Mobile App via Internet, and health providers reviewed the data to evaluate patient engagement and made system changes remotely on weekly basis in the first month and then monthly in the following three months.

The advanced HCL system (ICR 10 g, active insulin time (AIT) 3 hours and glucose target 110 mg/dl) improved TIR (70-180mg/dl) to 52% in two weeks of SmartGuard Auto Mode, where postmeals hyperglycemia was noted and the following changes were performed: ICR 7gr, AIT 2 hours, and glucose target 100 mg/dl. HbA1c decreased from 8.6% (70 mmol/mol) before to 6.7% (50 mmol/mol) three months after advanced HCL initiation. TIR (70–180 mg/dl) improved above 70% in the first month, reaching 73% in the third month of Auto Mode initiation (Figure 1). Increased growth velocity (predicted 7.2 cm/y) was also noted during the advanced HCL treatment (Table 1).

The participant used the sensor for 95% of the time and spent a 91% in SmartGuard Auto Mode during the observation. We did not find significant difference in hypoglycemic events and sensor wear during the study period.

Hyperglycemic patterns, noted during MDI and GH treatment, were diminished using advanced HCL in SmartGuard Auto Mode, which were more pronounced throughout the nighttime (Figure 1).

3 | DISCUSSION

Despite some limitations, we have provided a general overview of a positive effect on Hba1c from the use of the advanced HCL in a young male with T1D and short stature treated with GH.

The reduction in HbA1c to 6.7% (50 mmol/l) by almost 2% (21.9 mmol/mol) after initiation of advanced HCL system observed in our participant is greater than previous studies have demonstrated (0.3% reduction in Hba1c within the first six months after GH treatment in participants with T1D on MDI or CSII[2]). Moreover, a similar study reported an increase in HbA1c by 0.6% in the first year of GH treatment in T1D.[3] The HbA1c target of <7.0% (53 mmol/mol) established by the ADA and ISPAD guidelines for glycemic control in children was reached in our case.[5,6]

In our case, TIR (70-180 mg/dl) decreased by almost 30% in the first year on the GH treatment on MDI with CGM, then subsequently increased to 72.3%, three months after initiation of advanced HCL system, which is higher than 67% achieved with similar advanced HCL system in adolescents and young adults with T1D without GH treatment.[7] Time in range, time below, and above range observed in our participant, all achieved the desired clinical targets for CGM data interpretation.

Over the 15-month GH treatment period in our analysis, daily insulin requirements increased significantly from 0.8 to 1.1 μ/kg with MDI and then to 1.2 μ/kg with advanced HCL system, which is comparable to other
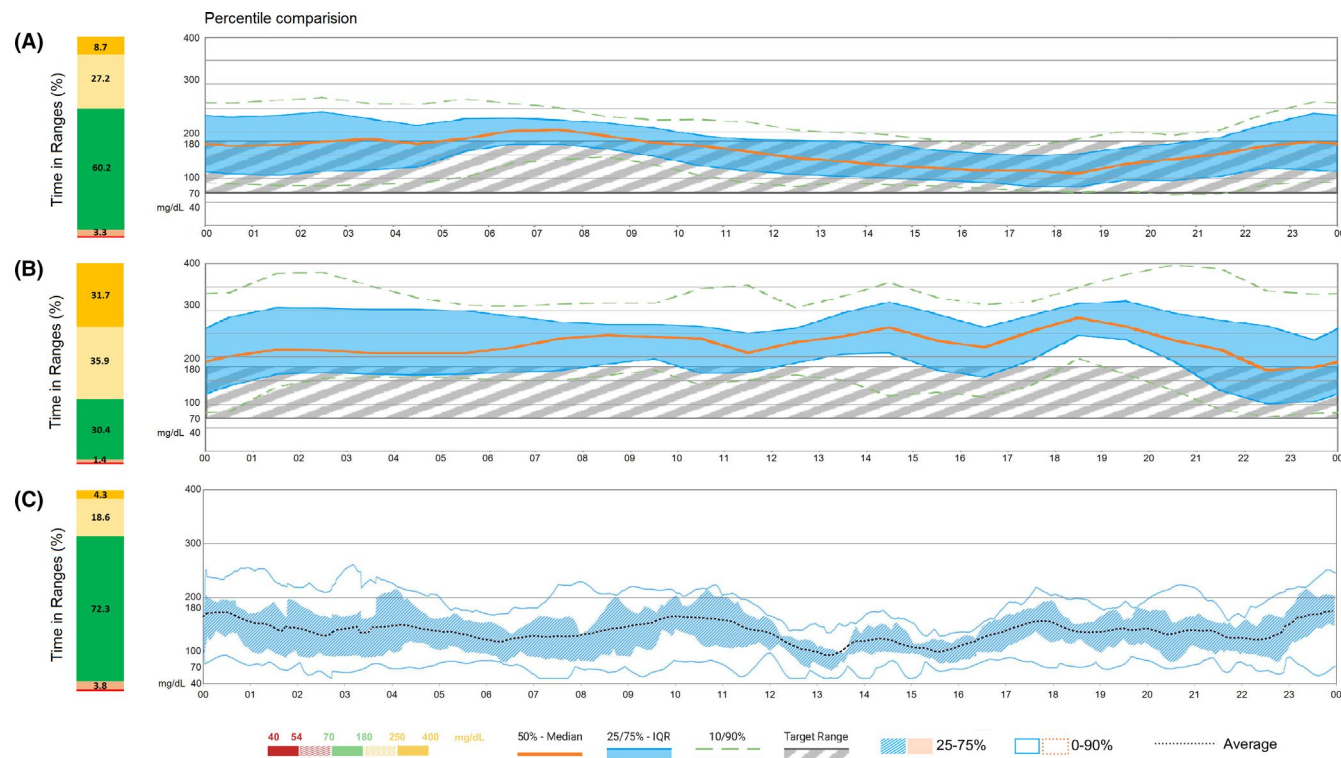
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FIGURE 1 Ambulatory glucose profile and time in ranges in participant with T1D and GH deficiency, before and during GH treatment on different therapy: MDI and advanced HCL system. Values are shown as percentage spent in ranges during the interval: (A) MDI, 90 days before initiation of GHT; (B) MDI +GHT, 90 days before AHCL initiation; (C) AHCL+GHT, 90 days. TIR (70–180 mg/dl): 60.2% on MDI, 30.4% on MDI+GHT and 72.3% on AHCL+GHT; glucose values <54mg/dl are not shown on the graph: 0.6% on MDI and MDI+GHT and 1.0% on AHCL+GHT. Blue area: SG 25–75% IQR; orange line: SG median; dotted black line: SG median. AHCL, advanced hybrid closed loop; GH, growth hormone; GHT, growth hormone treatment; IQR, interquartile range; MDI, multiple daily injections; TIR, time in range; SG, sensor glucose

findings 0.7 to 1.0 u/kg after 6 months[2] and 0.7–1.1 µ/kg after 2 years GH treatment.[8]

Advanced HCL system characteristics (Auto Mode usage, sensor wear, and calibrations) and strengthening the ICR by 20–30% found in our report were comparable to previously published results in adolescent and young people with T1D.[7]

Growth response in the first year of GH treatment in our observation showed improved height SDS by 0.7 SDS, which was comparable to 0.8 SDS (−2.6 to − 1.9 SDS) over one year GH treatment,[5] but higher than 0.3 SDS.[3] Expected growth velocity over 4 cm/year was observed in our case (6–7 cm/year) which was comparable to other findings (7–8 cm/year) in children with T1D and GH treatment.[8] GH dosage on average 0.2 mg/kg/week[8] was also observed.

Stringent patient selection criteria are crucial for successful CSII management, which include individual's responsibilities such as monitoring blood glucose at least four times per day, ability to accurately count carbohydrates, and appropriate management in response to hypoglycemia or hyperglycemia. Individual's motivation to improve glycemic control and communication with

diabetes team are additional points for successful pump initiation. We offer pump therapy to all patients with T1D, and once the above conditions are met, insulin pump therapy will be initiated. In our case, additional concern for initiating the advanced HCL system was the burden of two conditions (T1D and GH deficiency) and their management (glucose monitoring, insulin and GH injections, frequent correction doses for hyperglycemia), which was considered as a motivation for improvements in glycemic control.

The improved clinical outcomes observed in our case were achieved in a safe manner, with no DKA events or severe hypoglycemia during the initiation period and subsequent observation period of advanced HCL system. No significant side effects of GH treatment were reported, and good GH treatment compliance was similar to previous reports.[2]

The improved clinical outcomes in our report were likely driven by the high sensor and Auto Mode use, parental/guardian motivation, involvement and supervision of the young person, support and follow-up by the diabetes team, as well as the system algorithm technology with automatic adjustment of basal insulin delivery

and automatic insulin bolus corrections for high glucose levels.

Limitations in our case include short follow-up period with advanced HCL system and single patient experience. However, the objective of this research was to present the use of this novel advanced HCL technology as an alternative method to improve glycemic control in patient with T1D and GH treatment.

GH treatment is safe in patients with T1D and GH deficiency. Higher insulin demands can be adjusted accordingly as required. Pre-existing T1D in children should not be a barrier to initiate GH treatment if needed.[9]

4 | CONCLUSION

Initiation of advanced HCL, in people with T1D and GH treatment, can be an effective tool to improve glycemic control and decrease patient's health burden without further increasing total daily insulin requirements. Further clinical trials should be performed to confirm our findings.

CONFLICTS OF INTEREST
No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS
G.P. designed the study. G.P., J.C., and M.P. collected the data. G.P. and J.C. researched the data. G.P., F.A., J.C., E.D., and K.H. contributed in writing the manuscript. G.P. is the guarantor of this work and, as such, had full access to all the data in the report and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICAL APPROVAL
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local Ethics Committee, and the participant and his guardians signed a written informed assent/consent before the start of study-related procedures.

INFORMED CONSENT
Informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT
The data that support the findings of this analysis are available from the corresponding author upon reasonable request.

ORCID
Goran Petrovski https://orcid.org/0000-0002-8622-2186

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