# CLINICAL CARE AND TECHNOLOGY



# First year on commercial hybrid closed-loop system experience on 111 children and adolescents with type 1 diabetes

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### Abstract

**Objective:** The hybrid close-loop system (HCL) is a rapidly emerging treatment method for type 1 diabetes (T1D), but the long-term effectiveness of the system remains unclear. This study investigates the influence of the HCL on glycemic control in children and adolescents with T1D in a real-life setting during the first year on HCL.

**Research design and methods:** This retrospective study included all the patients (n = 111) aged 3 to 16 years with T1D who initiated the HCL system between 1st of December 2018 and 1st of December 2019 in the Helsinki University Hospital. Time in range (TIR), HbA1c, mean sensor glucose (SG) value, time below range (TBR), and SG coefficient of variance (CV) were measured at 0, 1, 3, 6, and 12 month. The changes over time were analyzed with a repeated mixed model adjusted with base-line glycemic control.

**Results:** After the initiation of HCL, all measures of glycemic control, except HbA1c, improved and the effect lasted throughout the study period. Between 0 and 12 month, TIR increased ( $\beta = -2.5$  [95%CI: -3.6 - (-1.3)], p < 0.001), whereas mean SG values ( $\beta = -0.7$  [95%CI: -0.9 - (-0.4)]), TBR ( $\beta = -2.5$  [95%CI: -3.6 - (-1.3)]), and SG CV ( $\beta = -4.5$  [95%CI: -6.3 - [-2.8]) decreased significantly (p < 0.001). Importantly, the changes occurred regardless of the age of the patient.

**Conclusions:** Measurements of glycemic control, except HbA1c, improved significantly after the initiation of the HCL system and the favorable effect lasted throughout the follow-up. These results support the view that HCL is an efficacious treatment modality for children and adolescents with T1D of all ages.

### KEYWORDS

glycemic control, hybrid closed-loop system, type 1 diabetes

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# 1 | INTRODUCTION

Multiple studies have shown that HbA1c levels above 53 mmol/mol or 7% increase the risk of microvascular complications even in the pediatric population with type 1 diabetes (T1D).<sup>1</sup> Additionally, the International Consensus recommends therapeutic goals for time in range (TIR, 3.9–10 mmoL/L) of 70% or more, time below range (TBR < 3.9 mmoL/L) of less than 4%, and CV of less than 36%.<sup>2,3</sup> Achieving these goals is challenging, especially in children and adolescents with T1D who commonly suffer from diabetes distress.<sup>4–6</sup> Additionally, hormonal changes of puberty are known to complicate diabetes management during adolescence.<sup>7</sup> Although the proportions of patients on continuous subcutaneous insulin infusion (CSII) and continuous glucose measurement (CGM) have increased, glycemic control has not improved.<sup>8,9</sup> Thus, the need for more efficacious and easier treatment modalities is evident, and automated insulin infusion algorithms have been designed for this purpose.

The first commercially approved HCL system (Minimed 670G, Medtronic, Northridge, California) was launched in Finland in late 2018. In this system, the target sensor glucose (SG) is set to 6.7 mmoL/L (120 mg/dl), and the algorithm monitors SG values every 5 min with an adjustment in basal delivery of insulin.<sup>10</sup> The carbohydrate-insulin ratios and active insulin time can be adjusted, and the patient uses the Bolus calculator to administer the correct dose of insulin for meals. The safety and efficacy of the system have been proved in several short-term studies, but there are only few studies in children with longer follow-up.<sup>11,12</sup> The purpose of this study was to evaluate how the first commercial hybrid close-loop (HCL) system works in a real-life setting in children and adolescents during the first 12 months of treatment. We hypothesized that the HCL system would result in improved TIR and less glycemic variability in children and adolescents with T1D.

# 2 | PATIENTS AND METHODS

This retrospective register study was conducted at four pediatric diabetes outpatient clinics of Helsinki University Hospital (New Children's Hospital, Jorvi hospital, Lohja hospital and Porvoo hospital). Altogether, 111 children and adolescents (aged 3 to 17 years) with T1D started the Minimed 670G HCL system between 1st of December 2018 and 1st of December 2019 and were included in this study. The criteria for starting Minimed 670G HCL system were the capability to (i) use CGM (including calibration) over 70% of the time (based on Carelink, Diasend or Libreview downloads, depending on what CGM or iCGM patients used before), (ii) use Bolus Calculator, count carbohydrates and take boluses before meals, and (iii) trust the algorithm. Patients not familiar with the real time CGM practiced 2-4 weeks the Guardian Sensor 3 as a standalone CGM before starting CSII. The exclusion criterion for Minimed 670G use was a total daily dose (TDD) of insulin under 8 units/day. Minimed 670G HCL system was also used in children under 7 years old, if the clinician considered this treatment to be beneficial for patient and family

**TABLE 1**Characteristics of 111 children and adolescents withtype 1 diabetes who initiated a hybrid closed loop insulin pump

|                             | Number (%) |  |  |
|-----------------------------|------------|--|--|
| Gender                      |            |  |  |
| Males                       | 67 (60.4)  |  |  |
| Females                     | 44 (39.6)  |  |  |
| Age, years                  |            |  |  |
| 0-6.9                       | 17 (15.3)  |  |  |
| 7-11.9                      | 63 (56.8)  |  |  |
| 12-16                       | 31 (27.9)  |  |  |
| CSII                        | 86 (77.5)  |  |  |
| MDI                         | 25 (22.5)  |  |  |
|                             | Mean (SD)  |  |  |
| HbA1c at baseline, mmol/mol | 57.8 (8.5) |  |  |
| Hba1c at baseline, %        | 7.4 (0.8)  |  |  |
| Diabetes duration, years    | 5.1 (2.5)  |  |  |
| Automode use at 3 month, %  |            |  |  |
| 0–6.9 year                  | 95 (2.7)   |  |  |
| 7-11.9 year                 | 88 (14.3)  |  |  |
| 12-16 year                  | 80 (13.0)  |  |  |
| Automode use at 12 month %  |            |  |  |
| 0-6.9 year                  | 92 (7.8)   |  |  |
| 7–11.9 year                 | 85 (15.6)  |  |  |
| 12-16 year                  | 75 (16.1)  |  |  |

Abbreviations: CSII, continuous subcutaneous insulin injection; MDI, multiple daily injections.

agreed on off-label use of the system. In Finland, pediatric T1D patients attend publicly funded health care with a nominal outpatient clinic fee, which includes also the CGM and insulin pump treatment. The technical education of the system was given by Medtronic product specialist in one 2 h session. The medical education was given during standard visits in Diabetes outpatient clinic. No additional educational program was used. After initiating the system, the CGM download was checked routinely after 1 month, and after that during normal clinical visits. If patients needed help with settings, the CGM downloads were remotely evaluated.

The main outcome measures for this study were the changes in TIR, HbA1c, TBR, mean SG value, and SG CV during the first year. The data was gathered from electronic patient records documented during routine outpatient clinic visits. The baseline characteristics of the study population are shown in Table 1. The CGM measures of glycemic control (TIR, TBR, mean SG, SD, and CV) were collected before starting the system, and at 1, 3, 6, and 12 months after the initiation of the HCL system. Glucose management indicator (GMI) was assessed 1 and 12 months after starting the insulin pump. HbA1c (Afinion, Abbott) was examined before starting the system and at 3, 6, and 12 months. The TDD and proportion of basal/boluses were evaluated before the treatment and at 3, 6, and 12 months. The time in Auto Mode was calculated at 3 and 12 months. Of the 111 participants, 59 (53%) used Guardian –CGM, 51 (46%) used iCGM, and one (1%) used Dexcom. The COVID-19 pandemic affected our outpatient clinic: in Finland, the lockdown period started March 22nd and lasted until May 20th 2020. During this time, the diabetes outpatient clinic had mainly virtual visits, and only a few laboratory tests were performed. This resulted in missing HbA1c values at 6 months and at 12 months.

The Ethics Committee of Helsinki University Hospital approved the study and a research permit was also obtained from the Helsinki University Hospital. The principles of Good Clinical Practice and the Declaration of Helsinki were followed.

### 2.1 | Statistical analyses

The data are presented with mean (SD) or mean (95% confidence interval). Analyses were performed with SPSS statistic for Windows (version 25.0, Chicago, IL). A linear mixed model was used in repeated measures analyses. In the model, time, gender, age group, or prior treatment modality were used as fixed effects. Time by gender, age group, or prior treatment modality interactions were included in the model to examine whether the mean change over time was different between the groups. The analyses were adjusted with the baseline glycemic control, thus the HbA1c measured prior to HCL initiation was included in the model as covariate. The data included missing values, but they were assumed to be completely random, and the normal distribution assumption of the data was checked from studentized residuals. Additionally, we evaluated how the effect of the HCL lasted by analyzing the changes (i.e., deltas) of the main outcome measures between 0 and 12 months with a one sample t-test. The same test was used when the use of Auto Mode between 3 and 12 months was evaluated. Between group comparisons of the outcome measures were performed with an independent samples t-test (two groups) or with ANOVA (three groups). Correlations were analyzed using the Pearson correlation. We performed sensitivity analyses to adjust for the missing HbA1c values, thus the main outcome measures were also analyzed from the 70 participants with a complete HbA1c data set. The level of statistical significance was set to p-value less than 0.05.

# 3 | RESULTS

The study cohort included 111 patients (60.4% males) (Table 1). The mean age of the participants was 9.7 (3.2 SD) years and the mean duration of diabetes was 5.1 years (2.5 SD). The baseline characteristics of the patients including measurements of glycemic control are presented in Table 1. At baseline prior to the HCL, the males (n = 67) had higher TBR (mean 7.0% [6.1 SD]) and SG CV (42% [7.4 SD]) than the females (n = 44) (4.1% [4.0 SD], p = 0.013 and 38% [8.0 SD], p = 0.023, respectively), whereas the patients on CSII (n = 86) had higher HbA1c (59 mmol/mol [7.4 SD]/7.6% [0.7 SD]) and mean SG values (9.7 mmoL/L [1.2 SD]) and lower TBR (4.3% [3.6 SD]) than the

subjects on MDI (n = 25) (52 mmol/mol [9.5 SD]/6.9% [0.9 SD] p < 0.001, 8.6 mmoL/L [1.7 SD], p < 0.001, and 10.1% [7.4 SD], p = 0.001, respectively). CSIIs with suspend before low feature showed (n = 48) lower TBR (3.3% [3.1]) than those without (n = 19) (6.7% [3.8], p < 0.001). At the same time, the oldest age group (12-16 year, n = 31) had higher HbA1c (62 mmol/mol [10.7 SD]/7.8% [1.0 SD]) and mean SG value (10.0 mmoL/L [1.6 SD]) than the patients aged 7 to 11.9 years (n = 63) (56 mmol/mol [7.1 SD]/7.3% [0.3 SD], p = 0.010 and 9.2 mmoL/L [1.2 SD], p = 0.041, respectively). Between 0 and 12 months, none of the participants had diabetic ketoacidosis, but a 15-year-old patient had one severe nocturnal hypoglycemia after disconnecting the CGM at bed-time for unknown reason.

## 3.1 | Main outcome measures

After the initiation of HCL, the measures of glycemic control improved rapidly, and the favorable effect lasted for 12 months of follow-up (Figure 1) (Table 2). Indeed, the initial changes (0–1 months) in TIR and mean SG correlated well with respective changes between 0 and 12 months (r = 0.70 and r = 0.70, respectively, p < 0.001 for both).

TIR increased significantly over 12 months of follow-up ( $\beta = 11.6$  [95%CI: 8.9–14.2], p < 0.001) and between 0 and 12 months (mean change 11.9%, p < 0.001) (Figure 1). No significant difference in the changes of TIR was found between genders (p = 0.55), prior treatment modality (p = 0.94) or age group (p = 0.25, Figure 1). The decreasing trend in HbA1c failed to reach significance (p = 0.069) (Figure 1), and no significant difference was found in HbA1c over time between age groups (p = 0.51), gender (p = 0.29), or prior treatment method (p = 0.071).

TBR decreased significantly over 12 months of follow-up ( $\beta = -2.5$  [95%CI: -3.6 - (-1.3)], p < 0.001) and between 0 and 12 months (mean change -2.7%, p < 0.001) (Figure 1). Prior MDI treatment associated with a decrease in TBR over 12 months of follow-up ( $\beta = -6.4$  [95%CI: -3.6 - (-1.3)], p < 0.001), whereas a similar significant change was not observed in subjects previously on CSII (p = 0.053). No significant differences in TBR were observed over time between gender (p = 0.50) and age groups (p = 0.90).

In all patients, mean SG values decreased significantly over 12 months of follow-up ( $\beta = -0.7$  [95%Cl: -0.9 - (-0.4)], p < 0.001) and between 0 and 12 months (mean change -0.6 mmoL/L, p < 0.001) (Figure 1). No significant difference was observed over time between males and females (p = 0.135) or age groups (p = 0.17). SG CV decreased during the follow-up ( $\beta = -4.5$  [95%Cl: -6.3 - [-2.8]), p < 0.001), and between 0 and 12 months (mean change -4.6, p < 0.001) (Figure 1). Male gender associated with increased SG CV between 3 and 12 months ( $\beta = 2.2$  [95%Cl: 0.5-3.9], p = 0.012). No significant difference was observed between age groups (p = 0.92) or prior treatment modalities (p = 0.122).

Finally, we evaluated the relationship between the time spent in Auto Mode and measures of glycemic control. At 3 months,



**FIGURE 1** Mean (±SD) Time in range (A, F), HbA1c (B), Time below range (C), sensor glucose (SG) value (D), and SG coefficient of variation (CV) (E) in 111 children and adolescents with type 1 diabetes who initiated hybrid closed-loop system (HCL). *p* value is obtained from the repeated mixed model between 0 and 12 months, and in panel F *p*-value illustrates the time by age group interaction

time in Auto Mode correlated negatively with HbA1c (r = -0.22, p = 0.03). At 12 months, time in Auto Mode correlated negatively with HbA1c (r = -0.47, p < 0.001), mean SG value (r = -0.43, p < 0.001), the change in HbA1c between 0 and 12 months (r = -0.37, p = 0.001), and positively with TIR (r = 0.44, p < 0.001). Between 3 and 12 months, the patients had no significant changes in the time spent in Auto Mode (p = 0.09) (Table 2), whereas the use of Auto Mode decreased significantly in the oldest age group (p = 0.049) (Table 1).

In sensitivity analyses including the 70 participants with a complete HbA1c data set, the changes in all outcome measures remained significant (data not shown).

# 4 | DISCUSSION

In the current study, the CGM parameters of children and adolescents improved significantly after the initiation of the HCL, and the

| TABLE 2       | Changes in the measures of glycemic control in 111 children and adolescents with type 1 diabetes after the initiation of a hybrid |
|---------------|---|
| closed loop i | nsulin pump   |

|                          | n   | Prior to HCL | n   | 1 month    | n   | 3 month    | n   | 6 month    | n   | 12 month   | p value*  |
|--------------------------|-----|--------------|-----|------------|-----|------------|-----|------------|-----|------------|-----------|
| TIR, (3.9-10.0 mmoL/L) % | 93  | 55.7 (13.0)  | 106 | 67.9 (9.7) | 108 | 68.4 (7.7) | 106 | 67.7 (8.8) | 108 | 67.3 (8.6) | p < 0.001 |
| HbA1c, mmol/mol          | 111 | 57.8 (8.5)   |     | NA         | 104 | 55.2 (6.0) | 93  | 55.6 (6.0) | 86  | 56.6 (7.3) | p = 0.119 |
| HbA1c, %                 | 111 | 7.4 (0.8)    |     | NA         | 104 | 7.2 (0.6)  | 93  | 7.2 (0.7)  | 86  | 7.3 (0.7)  |           |
| Mean SG value, mmol/l    | 101 | 9.4 (1.4)    | 102 | 8.6 (0.8)  | 107 | 8.5 (0.7)  | 104 | 8.6 (0.8)  | 106 | 8.7 (0.9)  | p < 0.001 |
| TBR, (<3.9 mmoL/L), %    | 92  | 5.9 (5.5)    | 105 | 3.7 (2.5)  | 107 | 3.6 (2.6)  | 106 | 3.3 (2.8)  | 108 | 3.2 (2.6)  | p < 0.001 |
| SG CV, %                 | 90  | 40.7 (7.8)   | 100 | 37.5 (4.7) | 106 | 36.9 (5.6) | 105 | 37.0 (5.6) | 104 | 35.9 (5.5) | p < 0.001 |
| SG SD                    | 91  | 3.8 (0.9)    | 100 | 3.3 (0.6)  | 106 | 3.2 (0.5)  | 104 | 3.3 (0.6)  | 104 | 3.2 (0.6)  | p < 0.001 |
| Total insulin, IU        | 81  | 30 (17.9)    |     | NA         |     | NA         | 98  | 31 (18.4)  | 105 | 33 (18.3)  |           |
| Total insulin per weight | 83  | 0.7 (0.2)    |     | NA         |     | NA         | 98  | 0.7 (0.2)  | 101 | 0.7 (0.2)  |           |
| Basal insulin, %         | 82  | 43 (9.0)     |     | NA         |     | NA         | 99  | 43 (10.1)  | 105 | 44 (9.4)   |           |
| Bolus insulin, %         | 82  | 58 (12.2)    |     | NA         |     | NA         | 98  | 57 (10.6)  | 105 | 56 (9.3)   |           |
| Time in automode, %      |     | NA           |     | NA         | 101 | 87 (13.7)  |     | NA         | 103 | 84 (15.7)  |           |

Note: Mean (SD).\* p values refers to comparison of the change between prior to HCL and 12 months visit against zero (one-sample t test). Abbreviations: CV, coefficient of variation; SG, sensor glucose; TBR, time below range; TIR, time in range.

favorable result remained after 12 months of treatment. In particular, TIR improved rapidly after the initiation of the HCL regardless of age. A similar phenomenon has been reported in both 7- to 13-year-old and under 7-year-old children from the United States and Israel.<sup>13,14</sup> However, to the best of our knowledge, this is the first study of a commercial HCL system in children under the age of 7 years with 12 months of follow-up. Furthermore, our youngest patient cohort (under 7 years) had higher TIR than the one reported by Salehi and co-workers after 6 months on HCL.<sup>14</sup> The reason for this difference is not clear. Since the mean SG. SD. and CV were lower and TBR higher in our study prior the initiation of HCL system, one explanation might be that the Finnish caregivers were not afraid of hypoglycaemia. Furthermore, nearly all the children in our study were using CGM already before starting the HCL system. No episodes of serious hypoglycaemia in Auto Mode were observed during the follow-up, even though TIR increased. In fact, after starting the HCL, TBR decreased, which is contrary to the results reported in young children treated with HCL.14

Remarkably, our patients stayed persistently in Auto Mode during the follow-up. This was also evident in teenagers: a year after the beginning of the study, they were on Auto Mode 75% of the time. In the previous studies, the use of Auto Mode has been 72% after 3 months and only 38.5% during 6 months of follow-up.<sup>15,16</sup> The difference is not explained by the baseline glycemic control, since Duffus et al. reported a baseline HbA1c of 67 mmol/ mol or 8.3%, which was very similar to the one in our patient cohort (64 mmol/mol or 8.0%).<sup>16</sup> In our clinic, if patient has no experience on CGM that requires calibrations, we use the Guardian CGM 2–4 weeks as a standalone CGM without CSII to ensure correct use. This might contribute to the more sustained use of Auto Mode in this study. The explanation for low Auto Mode use in the previous studies remains unclear. In our cohort, only one

patient stopped using the HCL system. In the earlier studies for children and adults, drop-out rates up to 33% have been reported during a study period of 6 to 12 months.<sup>12,17,18</sup> Reasons for discontinuing treatment were mostly related to technical issues with the sensor use, or Auto Mode exits and difficulties in maintaining the Auto Mode. After these studies, changes were made to transmitter's sensor algorithm. Minimed 670G sensor algorithm used in Europe included modifications that reduced exits into manual mode (Ohad Cohen, Medtronic, personal communication).Thus, the different algorithm might have contributed to the improved outcomes in Finland, though other factors such as pre-meal bolusing, carb content, and carb counting skills—have probably contributed substantially more.

The importance of glucose variability in the development of long-term complications of diabetes has been acknowledged, and CV under 36% has been chosen to reflect stable glycemic control.<sup>3</sup> Wide variability in SG levels results in hypo- and hyperglycaemia and may induce vascular damage in the long-term.<sup>19</sup> In our population, CV and TBR improved in all age groups significantly and rapidly after starting the HCL, and the results remained stable after the follow-up providing hope for a healthy future for children and adolescents with T1D.

There are several limitations in this study, the most obvious one being the retrospective design. The selection of study participants might have caused a bias concerning superior glycemic control. Thus, the results may not be translated to patients who do not fulfill the inclusion criteria. The data reflect experience in the highstandard health care system and, thus, the results may not completely be generalized to other health care systems or to every patient with T1D, particularly if the patient is not familiar with carbohydrate counting, does not take boluses before meals, nor trust the algorithm. Furthermore, the data included some missing values, which may have influenced the results. Finally, we did not assess the health-related quality of life in our patients, which would have been an important outcome of HCL treatment.

Our study is the largest HCL study including a year of followup performed on the pediatric population.<sup>11,12</sup> This was a retrospective study, which had no strict exclusion criteria on previous HbA1c levels or treatment modalities. The HCL systems were started at a single two-hour outpatient clinic visit if the patient had experience on CSII use, or during a three-day hospital visit if the patient was on MDI. This guidance period was shorter than reported previously,<sup>20</sup> and we had no special educational program for these patients, which may have influenced the results. Thus, the optimal length and structure of the guidance to the use of the HCL needs to be investigated further.

Despite the growing use of CGM and CSII, glycemic control of children has not improved simultaneously.<sup>8,9</sup> It is well known that a good blood glucose control already in childhood lowers the risk of diabetes complications in adulthood.<sup>21</sup> Based on our results, HCL systems may bring the much-needed aid to this quest and our results support the view that the HCL treatment will produce a paradigm shift in the management of T1D.

# 5 | CONCLUSIONS

The use of the hybrid closed-loop system appears to improve glycemic control of children rapidly after initiation and this positive effect persists during a year of follow-up. Finally, improved glycemic balance is achievable in children with T1D. The HCL systems with more advanced algorithms are likely to result in even more improved glycemic control and hopefully lower rates of diabetic complications in the future.

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### CONFLICT OF INTEREST

Anna-Kaisa Tuomaala has received lecture and consultation honoraria from Medtronic Diabetes Finland and EMEA, and is a member of Medtronic advisory board in Finland. Mari-Anne Pulkkinen has received a lecture honoraria from Medtronic Diabetes Finland.

### AUTHOR CONTRIBUTION

Anna-Kaisa Tuomaala was responsible for the concept and design of the study. Anna-Kaisa Tuomaala, Matti Hero, Päivi J. Miettinen supervised the study. All authors contributed to data acquisition, analysis, or interpretation. Tero Varimo and Anna-Kaisa Tuomaala carried out statistical analysis. The manuscript was drafted by Tero Varimo, Anna-Kaisa Tuomaala, Mari-Anne Pulkkinen, and Elina Hakonen. All authors revised the manuscript critically and approved the final version.

### ETHICS STATEMENT

The Ethics Committee of Helsinki University Hospital approved the study and a research permit was also obtained from the Helsinki University Hospital. The principles of Good Clinical Practice and the Declaration of Helsinki were followed.

### DATA AVAILABILITY STATEMENT

Anonymised individual-participant data that underlie the primary endpoints of this study will be made available 12 months after publication to investigators of methodologically reliable meta-analyses. Proposals may be submitted up to the senior author (annakaisa.tuomaala@hus.fi). Data will be shared according to the EU General Data Protection Regulation and national and hospital data protection regulations.

### PEER REVIEW

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