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Glycemic control in people with type 1 diabetes using a hybrid closed loop system and followed by telemedicine during the COVID-19 pandemic in Italy

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ABSTRACT

Aims: This study aims at evaluating the metrics of glycemic control in people with type 1 diabetes using the hybrid closed loop (HCL) system during the COVID-19 lockdown.

Methods: This is a retrospective study of thirty adults with type 1 diabetes using HCL and followed with telemedicine at an Italian University Hospital. Data on metrics of glucose control were collected at different times: two weeks before the lockdown (Time 0), first two weeks of lockdown (Time 1), last two weeks of lockdown (Time 2) and first two weeks after the lockdown (Time 3). The primary endpoint was the change in glucose management indicator (GMI) across the different time points.

Results: GMI did not worsen over time (Time 1 vs Time 3, 7% vs 6.9%, $P < 0.05$), whereas a reduction of mean glucose ($P = 0.004$) and indices of glucose variability was observed. Time in range (TIR) significantly increased (68.5% vs 73.5%, $P = 0.012$), and time above range (TAR) level 2 (251–400 mg/dL) significantly decreased ($P = 0.002$). The improvement of TIR and glucose variability was mainly observed in participants < 35 years.

Conclusions: Adults with type 1 diabetes using HCL showed a significant improvement of most of the metrics of glucose control during the COVID-19 lockdown.

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1. Introduction

The therapy of type 1 diabetes still remains a clinical challenge for physicians, as a lifelong management is required to optimize glycemic control. Engaging in effective diabetes self-management often requires a great attention to meals, regulating insulin doses, planning physical exercise or working activities and facing psychological stress [1]. The recent innovations in technologies aimed at diabetes management have largely enhanced the ability to improve glycemic control with glucose sensing, glucose-responsive insulin delivery systems and tools for data management which lessened the burden of self-care [2,3].

Hybrid closed-loop (HCL) systems (also called artificial pancreas or automated insulin delivery systems) use a control algorithm that automatically and continually modulates the basal insulin infusion rate to regulate glucose levels to a target sensor glucose (SG) amount [4,5]. The standard target SG setting is 120 mg/dL, which can also be set temporarily to 150 mg/dL for exercise and other events. However, the user must still calculate carbohydrate intake and administer insulin meal boluses. Meta-analyses of randomized controlled trials comparing artificial pancreas systems with control therapy (conventional pump therapy or sensor-augmented pump therapy) in outpatient settings, reported that closed-loop systems were associated with an increased percentage of time in the normoglycemic range and reduced time spent in hyperglycemia and hypoglycemia, with a modest decrease in HbA_{1c} levels [6,7]. Moreover, evidence from observational retrospective studies showed an improvement of both time in range and HbA_{1c} in people switching from sensor-augmented pump to HCL system [8,9]; of note, the highest benefits in term of glycemic control seem to be related to the “auto-mode” utilization [10].

Since December 2019, the outbreak of the Coronavirus Disease 2019 (COVID-19), due to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally, affecting progressively more than 200 countries [11]. In order to limit the massive spread of the infection, in March 2020 the Italian Government declared the almost complete lockdown of Italy, since it was the second most affected country worldwide [12]. In response to the quarantine, most of the outpatient clinics dedicated to diabetes care were closed and diabetes services were largely transitioned to a telehealth/telemedicine model of care. On the other hand, the lockdown-induced reduction of outdoor activities with the related increase of sedentary behavior might have produced detrimental effects on glycemic control of people living with type 1 diabetes.

Downloading data from devices as HCL systems to the cloud enables users to review summary statistics and to visualize and share patterns of glucose levels, providing the healthcare professionals with an opportunity of interaction with patients during the lockdown. Interestingly, remote monitoring and reviewing of glycemic data by telemedicine are associated with significantly reduced levels of HbA_{1c} in people with type 1 diabetes [13,14].

This study is aimed at examining glycemic control before, during and after the lockdown against the spread of SARS-CoV-2 in a cohort of people with type 1 diabetes using HCL in a dedicated center for diabetes care of Southern Italy.

2. Materials and Methods

The present study represents a retrospective analysis of people with type 1 diabetes followed at Diabetes Unit of the University Hospital “Luigi Vanvitelli” in Naples (Italy) who were using a HCL therapy. As a retrospective study, the ethical approval was deemed unnecessary; however all patients gave their consent to their personal data being collected on the dedicated web-based cloud system (including health data) for scientific research.

2.1. Study participants

Men and women with type 1 diabetes were included in the study if they attended the Unit of Diabetes at the University Hospital Luigi Vanvitelli (Naples, Italy), were using the Medtronic MiniMed™ 670G for at least 6 months, had at least 80% coverage of the system in auto-mode, were sharing data on CareLink™ Personal (Medtronic), and had a telemedicine visit since May 18th, 2020. The CareLink™ platform enables users to link their personal accounts to those of the healthcare providers for the sharing and remote reviewing of data from diabetes devices; lifestyle information can also be entered. Patients would be excluded if they did not agree to be remotely connected to the Diabetes Unit or if they did not upload the data related to the two weeks before the Decree-Law of March 8th, which put the lockdown into effect. During the telemedicine visits, we collected information about the working status (studying at home, smart working or continuing working during the lockdown because of being involved in essential service), the levels of physical activity and other significant changes in lifestyle habits. We considered exercising for at least 3 h per week during the lockdown as regular physical activity.

2.2. Clinical variables and definition of periods

Age, sex, duration of diabetes, weight, body mass index (BMI), most recent glycosylated hemoglobin values, lipid profile, renal function parameters including urinary albumin excretion rate (UAER) and estimated glomerular filtration rate (eGFR) were collected for each patients from clinical medical records (Smart Digital Clinic, Meteda), as well as information about the presence of microvascular or macrovascular complications.

Data on glycemic control were extracted during the tele-visits from CareLink™ Personal reports, with an observation frame of two weeks from February 23rd to March 8th (Time 0, pre-lockdown phase), from March 9th to March 23rd (Time 1, first 2 weeks of lockdown phase), from April 20th to May 3rd (Time 2, last 2 weeks of lockdown phase), from May 4th to May 18th (Time 3, post-lockdown phase). For each period,

retrieved data included continuous glucose monitoring (CGM)-related metrics [mean glucose, standard deviation (SD), coefficient of variation (CV), glucose management indicator (GMI), percentage of sensor wear, percentage of time spent in the range of normoglycemia (TIR, 70–180 mg/dL), percentage of time spent below range (TBR, level 1 between 54 and 69 mg/dL, level 2 < 54 mg/dL), percentage of time spent above range (TAR, level 1 between 181 and 250 mg/dL, level 2 between 251 and 400 mg/dL)], information about HCL use (percentage of time spent in auto- and manual-mode), daily insulin dosage, expressed as basal and bolus rate, and the carbohydrates entered per day. Our primary endpoint was the change in GMI before, during and after the lockdown phase.

2.3. Statistical analysis

Descriptive statistics were used to characterize the study sample. Continuous variables are expressed as median and interquartile ranges (IQR) and categorical variables are presented as percentage. Repeated measure ANOVA analyses were performed for each variable, with Tukey's test correction, when needed. Variables registered before and after the lockdown were compared using the Wilcoxon Signed Rank Test. Statistical associations between variables were assessed using Spearman rank-order correlation test. Statistical significance was accepted at $P < 0.05$.

3. Results

A total of 30 patients (13 men and 17 women) has been included in the study. [Table 1](#) shows the demographic and clinical characteristics of the study population. The median age was 31.5 years (IQR 25–42) and the median BMI was 26.3 kg/m² [23–28]. Eight out of 30 patients were students; among the 22 remaining subjects 4 were teachers, 2 were lawyers, 13 were employees and only 3 patients were unemployed. All workers stayed at home in smart working; all students were engaged in distance learning. Six subjects (20%) had regular physical activity. The study population had a median HbA_{1c} level of 7.7% [7,8] and a median fasting plasma glucose of 124 mg/dL (113–182). Four patients had microvascular complications, of whom two had retinopathy, one had nephropathy and one had neuropathy. Participants used the HCL system in auto-mode for 91.5% of the time (90–96) and in manual mode for 8.5% (6–14), with a median sensor wearing of 91.5% of the time (90–96).

[Table 2](#) summarizes the main findings during the 4 periods analyzed. There was a significant increase in the percentage of time spent in auto-mode, which was higher in Time 3 [median (IQR), 94% (89–96)] than in Time 1 [89% (83–93)] ($P = 0.018$), along with a significant lower rate of manual mode over time ($P = 0.008$). GMI did not worsen over time, although a slight but significant reduction was observed between Time 1 [7% (6.8–7.4)] and Time 3 [6.9% (6.7–7.1)] ($P < 0.05$). Similarly, across the different time points, there was a significant reduction of mean glucose values ($P = 0.004$), SD ($P < 0.001$) and CV ($P = 0.024$). TIR significantly increased at Time 3 [73.5% (66–81)] as compared with both Time 0 [68.5% (65,74)] and

Table 1 – Baseline clinical characteristics of the population included in the study.

Variables	Type 1 diabetic patients (n = 30)
Age, years	31.5 (25, 42)
Diabetes duration, years	9.5 (6, 21)
Weight, kg	67 (66, 89)
BMI, kg/m ²	26.3 (23, 28)
M/F, n (%)	13 (17)
Smoking, n (%)	9 (30)
Students, n (%)	8 (27)
Patients with regular PA, n (%)	4 (13)
HbA _{1c} , %	7.7 (7, 8)
HbA _{1c} , mmol/mol	61 (53, 64)
Fasting plasma glucose, mg/dL	124 (113, 182)
SBP, mmHg	120 (120, 130)
DBP, mmHg	80 (70, 80)
Total cholesterol, mg/dL	165.5 (149, 196)
HDL, mg/dL	48 (44, 53)
LDL, mg/dL	98 (82, 118)
Triglycerides, mg/dL	62 (52, 91)
Creatinine, mg/dL	0.9 (0.7, 1.1)
UAER, mg/24 h	8 (5, 15)
Microvascular complications, n (%)	4 (13)

Data are expressed as median and interquartile ranges (IQRs) or number (percentage). BMI, Body mass index; DBP, diastolic blood pressure; F, female; HDL, high density lipoprotein; LDL, low density lipoprotein; M, male; PA, physical activity; SBP, systolic blood pressure; UAER, urinary albumin excretion rate.

Time 1 [71% (64–76)] ($P = 0.012$), whereas TAR level 2 significantly decreased at Time 3 [4% (2–8)] as compared with both Time 0 [6% (3–8)] and Time 1 [6% (3–11)] ($P = 0.002$). TAR level 1 together with both TBR level 1 and 2, remained unchanged during the study. Moreover, across the different time points, there was a significant change in the amount of carbohydrates assumed, which was highest at Time 1 ($P = 0.044$). No significant changes in total daily insulin dose were found, although the bolus rate moderately decreased and basal rate progressively increased over time. The six patients who continued to do physical activity during the lockdown showed similar trends over time in all the studied parameters, although the amount of carbohydrates entered per day was higher, and the total daily insulin dose was lower than those of the general population ([Table 3](#)).

At univariate analysis, the change in GMI inversely correlated with change in TIR ($r = -0.661$, $P < 0.001$) and positively correlated with change in TAR level 2 ($r = 0.629$, $P < 0.001$) and mean glucose values ($P < 0.001$) ([Table 4](#)). No significant correlations were found between the change in GMI and the change in SD and CV.

When dividing the study population according to age, we found that, at similar levels of HbA_{1c}, there was a significant improvement in TIR ($P = 0.018$) associated with a reduction in SD ($P = 0.041$) and CV ($P = 0.015$) in the 15 patients aged < 35 years, but not in those ≥ 35 years over time ([Table 5](#)). Moreover, a significant decrease in SD ($P = 0.041$) was found in participants aged ≥ 35 years. No other significant changes in the other metrics of glucose control were observed.

Table 2 – Change of metrics of glucose control and HCL-related parameters during the 4 periods analyzed in the study population.

Variables	Time 0 (pre-lockdown)	Time 1 (first two weeks of lockdown)	Time 2 (last two weeks of lockdown)	Time 3 (post-lockdown)	P
Auto mode, %	91.5 (90, 96)	89 (83, 93)*	91 (86, 93)	94 (89, 96)	0.018
Manual mode, %	8.5 (6, 14)	11 (7, 17)*	9 (7, 14)	6 (4, 11)	0.008
Sensor wear, %	91.5 (90, 96)	90.5 (85, 95)	91 (82, 95)	90.5 (87, 95)	0.377
GMI, %	7 (6.8, 7.3)	7.1 (6.8, 7.4)*	7 (6.8, 7.2)	6.9 (6.7, 7.1)	0.001
Mean glucose, mg/dL	155 (149, 164)	163 (149, 167)*	154.5 (150, 164)	153 (145, 163)	0.004
SD, mg/dL	54.5 (50, 62)*	51.5 (46, 62)*	50.5 (47, 58)*	46 (41, 57)	< 0.001
CV, %	34.1 (32, 36)*	32.7 (30, 35)	33.1 (30.7, 36.7)	31.2 (26.5, 34)	0.024
TIR (70–180 mg/dL), %	68.5 (65, 74)*	71 (64, 76)*	73 (69, 75)	73.5 (66, 81)	0.012
TAR level 1 (181–250 mg/dL), %	23 (19,24)	22 (18, 24)	21 (19, 24)	20 (15, 26)	0.197
TAR level 2 (251–400 mg/dL), %	6 (3, 8)*	6 (3, 11)*	5 (3, 9)	4 (2, 8)	0.002
TBR level 1 (54–69 mg/dL), %	1 (0,2)	1 (0, 1)	1 (0, 2)	1 (0, 2)	0.190
TBR level 2 (<54 mg/dL), %	0 (0,1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.183
Total daily insulin dose, U/day	53.5 (37, 65)	56 (36, 70)	59 (36, 70)	58.5 (34, 70)	0.309
Bolus rate, %	49 (42, 51)	46 (37, 48)	44 (40, 50)	45 (34, 50)	0.127
Basal rate, %	51 (48, 58)	53 (51, 62)	55 (50, 59)	54 (50, 65)	0.191
CHO entered per day, g	152 (134, 203)	171 (142, 195)	156 (133, 197)	152 (109, 204)	0.044

Data are expressed as median and interquartile ranges (IQRs). CHO, carbohydrates; CV, coefficient of variation; GMI, glucose management indicator; SD, standard deviation; TAR, time above range; TBR, time below range; TIR, time in range. *P < 0.05 vs Time 3

Table 3 – Change of metrics of glucose control and HCL-related parameters during the 4 periods analyzed in the six patients practicing physical activity during the lockdown.

Variables	Time 0 (pre-lockdown)	Time 1 (first two weeks of lockdown)	Time 2 (last two weeks of lockdown)	Time 3 (post-lockdown)
Auto mode, %	91 (90, 94)	89,5 (86, 94)	93 (93, 94)	93.5 (92, 95)
Manual mode, %	9 (6, 10)	10.5 (6, 14)	7 (6, 7)	6.5 (5, 8)
Sensor wear, %	88 (86, 94)	88.5 (84, 94)	86.5 (72, 88)	88.5 (88, 95)
GMI, %	6.9 (6.7, 7)	7.1 (7, 7.4)	6.9 (6.9, 7)	6.9 (6.6, 7.1)
Mean glucose, mg/dL	151 (145, 155)	159 (157, 167)	152 (151, 153)	151 (143, 156)
SD, mg/dL	51 (47, 56)	51 (48, 52)	50 (47, 50)	44 (44, 45)
CV, %	32 (32, 36)	30 (30, 33)	32 (30, 33)	28 (26, 31)
TIR (70–180 mg/dL), %	70 (65, 79)	71 (62, 71)	73 (71, 75)	77 (73, 81)
TAR level 1 (181–250 mg/dL), %	21 (18,26)	23 (23, 32)	20 (20, 24)	20 (13, 23)
TAR level 2 (251–400 mg/dL), %	4 (2, 5)	6 (5, 6)	4 (4, 5)	3 (3,4)
TBR level 1 (54–69 mg/dL), %	1 (1,3)	0 (0, 1)	1 (1, 2)	1 (1, 2)
TBR level 2 (<54 mg/dL), %	0 (0,1)	0 (0, 0)	0 (0, 0)	0 (0, 1)
Total daily dose, U/day	38 (32, 70)	36 (34, 70)	39 (35, 70)	35 (34, 65)
Bolus rate, %	50 (50, 51)	48 (47, 48)	50 (43, 51)	51 (34, 52)
Basal rate, %	50 (48, 50)	52 (50, 52)	50 (48, 56)	49 (47, 65)
CHO entered per day, g	206 (176,222)	215 (147,228)	210 (151,223)	205 (109,211)

Data are expressed as median and interquartile ranges (IQRs). CHO, carbohydrates; CV, coefficient of variation; GMI, glucose management indicator; SD, standard deviation; TAR, time above range; TBR, time below range; TIR, time in range.

4. Discussion

To the best of our knowledge, this is the first study evaluating glycemic control in a population of adults with type 1 diabetes using HCL system during the lockdown due to COVID-19 pandemic. Our data show that, compared with the pre-lockdown phase, the metrics of glucose control of participants in the study did not deteriorate over time; interestingly, most of

them, including mean glucose values, indices of glucose variability (SD and CV), TIR and TAR level 2, further improved in the first 2 weeks after the end of the quarantine. The improvement in TIR and glucose variability was driven mainly by changes observed in participants younger than 35 years, who also showed the highest GMI reduction (even if not significant), rather than those whose age was equal or higher than 35 years.

Table 4 – Correlation between change of GMI and different metrics of glucose control.

	r_{sp}	P
Δ TIR	−0.629	< 0.001
Δ TAR level 2	0.629	< 0.001
Δ mean glucose	0.597	< 0.001
Δ SD	0.339	0.066
Δ CV	0.241	0.198

CV, coefficient of variation; SD, standard deviation; r_{sp} , Spearman coefficient; TAR, time above range; TIR, time in range.

Type 1 diabetes is characterized by high intra- and inter-day glycemic excursions, which can be influenced by daily routine, dietary choices, level of physical activity and sedentariness, anxiety and psychologic stress [15,16]. The use of HCL actually requires the manual insertion of carbohydrate information from which the recommended insulin bolus is determined, the calibration of the sensor at least two times per day by measuring fingerpick glucose levels, the prompt responses to alerts or alarms, and the sporadic upload of data on the web-based platform to allow physicians to review the reports [17]. Despite the forced confinement and the anxiety related to lockdown, our patients using HCL system showed an improvement of metrics of glycemic control over time. Possible explanations for these results may be firstly recognized in healthier food choices and consumption of home-made meals, with a more accurate carbohydrates counting, and a more regular sleep-wake rhythm. Interestingly, the amount of carbohydrates introduced with the diet increased during the two first weeks of the lockdown, presumably as a consequence of the “overeating” related to the limitation of outdoors activities or the boredom feelings generated by the quarantine. On the other hand, we may speculate that the impossibility of doing physical exercise, together with the change of working conditions (smart working and distance learning), led patients to check regularly glycemic readings, give immediate response to alarms and alerts displayed on

the pump, and finally execute the correct number of scheduled calibrations per day. This is supported by the increased time spent in auto-mode which brought about an improvement of mean glucose values and indices of glucose variability.

The significant amelioration of metrics of glucose control was observed in the population under 35 years, who showed the best improvement in both GMI (from 7% to 6.7%, even if not significant due to the small number of individuals) and TIR (from 68% to 74%), associated with the reduction of indices of glucose variability, including SD and CV. There is evidence from short-term observational studies of improved glycemic control in adolescents and young adults with type 1 diabetes treated with the artificial pancreas [18,19], although the use of HCL declined over time in about thirty percent of individuals [18], suggesting that youth experience barriers in sustaining use of HCL. Our results may reflect a more incisive change of lifestyle habits imposed by the quarantine in young people (age range 21–28 years) rather than in older ones (age range 35–56 years), who presented a more stable glucose profile over time.

Another reason accounting for our results may be recognized in the continuity of care of people with diabetes through the telemedicine. The use of telehealth/telemedicine has been indicated by the regional government of the Campania county as the preferential modality of assistance for diabetic patients. Moreover, the immediate feedback provided by the physicians in response to the upload of glycemic data might have improved patients’ ability in the management of diabetes. On the other hand, we could speculate that the better results obtained in the population under 35 years old may depend on the major confidence in the use of technologies for the management of diabetes, including the use of telemedicine services.

The improvement of TIR was obtained without an increase in the time spent in hypoglycemia, but was associated with a significant reduction of TAR level 2, which expresses the time spent in the range of relevant hyperglycemia (251–400 mg/dL).

Table 5 – Change in metrics of glucose control between pre- and post-lockdown phases according to the age of participants in the study.

Variables	People < 35 years (n = 15)			People ≥ 35 years (n = 15)		
	Time 0 (Pre-lockdown)	Time 3 (Post-lockdown)	P	Time 0 (Pre-lockdown)	Time 3 (Post-lockdown)	P
GMI, %	7 (6.8, 7.1)	6.7 (6.7, 6.9)	0.130	7.1 (6.8, 7.3)	7.1 (6.7, 7.2)	0.622
Mean glucose, mg/dL	154 (148, 155)	146 (145, 152)	0.303	160 (150, 166)	156 (154, 163)	0.489
SD, mg/dL	55 (48, 56)	45 (40.5, 47)	0.041	54 (50, 62)	50 (41, 61)	0.041
CV, %	35.7 (32, 36)	31.4 (26, 32)	0.015	33 (32, 37)	30 (27, 34)	0.095
TIR (70–180 mg/dL), %	68 (65, 74)	74 (73, 81)	0.018	69 (61, 74)	69 (62, 82)	0.151
TAR level 1 (181–250 mg/dL), %	23 (19, 24)	17 (15, 22)	0.376	23 (19, 23)	23 (13, 29)	0.421
TAR level 2 (251–400 mg/dL), %	5 (3, 7)	3 (2, 7)	0.168	7 (3, 10)	6 (2, 9)	0.083
TBR level 1 (54–69 mg/dL), %	2 (0, 2)	1 (1, 2)	0.844	1 (0, 2)	1 (0, 2)	0.125
TBR level 2 (<54 mg/dL), %	1 (0, 1)	1 (0, 1)	0.952	0 (0, 1)	0 (0, 0)	0.813
CHO entered per day, g	155 (144, 203)	154 (132, 195)	0.191	150 (63, 211)	152 (127, 198)	0.762

Data are expressed as median and interquartile ranges (IQRs). CHO, carbohydrates; CV, coefficient of variation; GMI, glucose management indicator; SD, standard deviation; TAR, time above range; TBR, time below range; TIR, time in range.

Given that both TBR and TAR represent the principal epiphenomena of the exposure to extreme glucose values [20], the reduction of TAR occurred without increasing TBR resulted in a further control of glucose variability, expressed also by the significant reduction of SD and CV.

Data on glycaemic control in type 1 diabetes during SARS-CoV-2 lockdown are still limited. A recent Italian retrospective study evaluated the effects of prolonged COVID-19 restrictions on glycaemic control of 13 adolescents with type 1 diabetes using HCL system. Glycaemic control did not worsen in the first two weeks of lockdown, as compared with the 2 weeks before lockdown, but there was a significant improvement of both TIR (from 68% to 72%, $P = 0.039$) and TBR (from 2% to 1%, $P = 0.041$) [21]. Further data come from studies of patients using continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) [22,23]. In a study on a cohort of 207 Italian adults with type 1 diabetes, there was a significant improvement of the TIR associated with the reduction of glucose variability during the lockdown phase [22]. Finally, among 33 individuals with type 1 diabetes using FGM, there was an improvement of glycaemic control in people who stopped working during the lockdown, confirming that the slowing of daily routine activities may have a positive impact on type 1 diabetes management [23].

The main limitation of this study refers to the relative small number of subjects included. However, this sample is representative of a highly selected population using the most innovative technological device available for diabetes management. Moreover, we included patients with a relatively fair glycaemic control using the sensor for most of the time, which did not allow us to evaluate whether the same results would apply also to people with worse glucose control. Strengths include the reporting of real-life experience with a telemedicine approach during COVID-19 pandemic, the assessment of recognized “key metrics” for the evaluation of glucose control [20], the analysis of the glycaemic reports at different time points, including the pre-lockdown phase, the lockdown itself and the post-lockdown phase.

In conclusion, adults with type 1 diabetes using HCL system showed a significant improvement of most of the metrics of glucose control over the lockdown phase due to SARS-CoV-2 pandemic, suggesting that the use of artificial pancreas allowed patients to effectively manage diabetes, despite the change in lifestyle habits imposed by the quarantine.

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Author contributions

M.L. and P.C. conceived the study and wrote the manuscript. M.P., F.C., A.S. and M.G. collected data and contributed to writing the manuscript. G.B. contributed to the data analysis and reviewed the manuscript for intellectual content. K.E. and M.I.M. conceived the study, contributed to the data analysis, reviewed and edited the manuscript. All authors approved the final version of the manuscript. M.I.M. is the guarantor

of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Competing Interest

M.P. has held lectures for Abbott, Lifescan and Mundipharma. M.G. received honoraria from Roche. G.B. received honoraria for speaking at meetings for Roche and Novo Nordisk. K.E. received honoraria for speaking at meetings from Novartis, Sanofi-Aventis, Lilly, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Mundi Pharma, Roche, Abbott, Lifescan, and Theras, and received consultancy fee from Roche. M.I.M. has held lectures for Astrazeneca, Bruno, Mundipharma, Merck, Roche, and Abbott and received consultancy fee from Roche. Other authors declare no conflict of interest.

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