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The impact of strict COVID-19 lockdown in Spain on glycemic profiles in patients with type 1 Diabetes prone to hypoglycemia using standalone continuous glucose monitoring

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ABSTRACT

Aims: Spain has been one of the worst affected countries by the COVID-19 pandemic. A very strict lockdown at home was imposed with a tough restriction of mobility. We aimed to evaluate the impact of this exceptional scenario on glucose profile of patients with T1D prone to hypoglycemia using standalone continuous glucose monitoring.

Methods: Patients with T1D prone to hypoglycemia using multiple daily injections and either a Dexcom G5® or a Free Style Libre® CGM systems for at least 6 months under the funding of National Health Service were included in an observational, retrospective study. Data were collected in two periods: pre-lockdown (PL), February 23rd-March 7th and within lockdown (WL), April 1st-14th 2020. The primary outcome was the difference in the proportion of time in target glucose range of 70–180 mg/dL (TIR). Additional glucometric data were also analysed.

Results: 92 patients were included: 40 women, age 42.8 ± 3.9 years, disease duration of 23.1 ± 12.6 years. Seventeen patients used Dexcom G5® and 75 Free Style Libre®. TIR 70–180 mg/dL (59.3 ± 16.2 vs $62.6 \pm 15.2\%$), time > 180 (34.4 ± 18.0 vs $30.7 \pm 16.9\%$), >250 (11.1 ± 10.6 vs $9.2 \pm 9.7\%$) and Glucose Management Indicator (7.2 ± 0.8 vs $7.0 \pm 0.8\%$) significantly improved (PL vs WL, respectively, $p < 0.05$). Time in hypoglycemia remained unchanged.

Conclusions: Lockdown conditions imposed by the COVID-19 pandemic may be managed successfully in terms of glycemic control by population with T1D prone to hypoglycemia using CGM. The strict daily routine at home could probably explain the improvement in the time in glycemic target without increasing the time in hypoglycemia.

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1. Introduction

To respond to the generational public health crisis caused by the global Coronavirus disease 2019 (COVID-19) pandemic, a rushed, coordinated effort across many sectors of society deemed necessary [1]. Spain's Interior Ministry imposed a highly strict lockdown across the country in March 14th 2020, the so called "state of alert" period [2]. This imposed drastic and never seen before measures to fight the *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), forced people to be at home modifying their daily routines becoming them very unchanging but really challenging for people with chronic diseases [3].

Properly managing of glucose control by patients with type 1 Diabetes (T1D) is markedly influenced by lifestyle conditions which are determined by the interplay between an individual's personal characteristics, social interactions, socioeconomic and environmental living conditions [4]. The parameters most commonly analyzed in the assessment of lifestyle influence include physical activity and nutrition, including monitoring carbohydrate intake. However, other parameters that have to be taken into account include exposure to stressful life events at work and at home, sleep duration, and specific unhealthy behaviors [5,6].

The use of continuous glucose monitoring (CGM) with multiple daily injections (MDI) has shown a reduction in non severe and severe hypoglycemia in people with T1D prone to this adverse event [7–10]. These findings lend support to the wider adoption and national health system reimbursement of this technology in the management of this high-risk population.

We wanted to take advantage of the exceptional living conditions imposed by the strict lockdown due to COVID-19 pandemic crisis in Spain to evaluate its impact on glucose profile of patients with T1D prone to hypoglycemia using standalone continuous glucose monitoring, a critically vulnerable population.

2. Subjects, material and methods

2.1. Study design and patients

We performed an observational, retrospective study that involved reviewing the electronic medical records and databases of individuals with T1D followed at the Diabetes Unit, Endocrinology and Nutrition Department at Hospital Clínic of Barcelona. In the current analysis, patients with T1D using MDI of insulin and either a real time continuous glucose monitoring (rtCGM) Dexcom G5® (Dexcom, San Diego, CA, US) or a intermittently scanned continuous glucose monitoring (isCGM) Free Style Libre® (Abbott Diabetes Care, Witney, UK) for at least 6 months were included. We used anonymized (Clarity® or Libreview® platforms) data collected between two different periods: pre-COVID-19-lockdown (PL), from February 23rd to March 7th 2020 and within the COVID-19 lockdown (WL), from April 1st to April 14th 2020. The specific indication for starting standalone CGM therapy under the funding of the Catalan National Health Service was recurrent

severe and disabling hypoglycaemic episodes or hypoglycemia unawareness despite the use of MDI.

Demographic characteristics and clinical data were recorded from computerized clinical records. Data from 14 consecutive days within the periods mentioned above were collected from uploads from each patient including CGM data. Only downloads with a sensor use >70% in both periods were considered. The primary outcome of the study was defined as the difference between periods in the proportion of time spent in the target glucose range of 70–180 mg/dL (TIR). In addition to this, data regarding the mean and coefficient of variation (\leq and $>36\%$) of sensor-measured glucose concentrations over both periods, % time with glucose concentrations in hypoglycaemia (<70 mg/dL; <54 mg/dL) and hyperglycaemia (>180 mg/dL; >250 mg/dL), glucose management indicator (GMI), sensor use and number of scans per day were also obtained.

The study was approved by the Ethical Committee of Hospital Clínic de Barcelona, and all subjects gave informed consent.

2.2. Statistical analysis

We planned a study of a continuous response variable from matched pairs of study subjects. If the true difference in the mean response of matched pairs is 3.00 with a standard deviation (SD) of 10.00, we will need to study 90 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.80. The Type I error probability associated with this test of this null hypothesis is 0.05.

The results are presented as mean \pm SD or proportions. Comparisons between continuous variables were performed using a paired Student's *t*-test. Comparisons between categorical variables were performed using a McNemar's test. A *P*-value < 0.05 was considered statistically significant. Data analysis was carried out with SPSS software, v.25 (IBM SPSS Statistics, Armonk, NY).

3. Results

A total of 92 patients were included: 40 women, age 42.8 ± 13.9 and with disease duration of 23.1 ± 12.6 years. All of them were treated with multiple injections of insulin, long-acting insulin analogues as basal insulin and rapid-acting analogues as prandial insulin. Forty-two percent of them have an International standard classification of education (ISCED) level 6; Bachelor's or equivalent level. Regarding CGM systems, 17 were using Dexcom G5® and 75 Free Style Libre®. Full population clinical characteristics are described in Table 1.

As part of their routine clinical follow-up, 12 of the subjects were virtually attended during the lockdown. None of these visits were done during the two specific periods selected in the study and there was not proactive phone call requested by the patients within the selected periods. There were not clinically significant acute hypo or hyperglycemic complications during the study and none of the patients needed hospitalization.

Table 1 – Characteristics of patients.

Number of patients	92
Age (years)	42.8 ± 13.9
Gender (Men/Women)	52/40 (56.5%/43.5%)
Duration of Diabetes (years)	23.1 ± 12.6
Any type of retinopathy (%)	23.9
Any type of nephropathy (%)	9.8
Any type of CVD (%)	5.4
MDI (%)	100
Total Daily Long-acting Insulin dose (units per day)*	25.3 ± 14.1
Total Daily Rapid-acting Insulin dose (units per day)*	24.4 ± 8.6
Total Daily Insulin dose (unit per day)*	49.7 ± 19.0
Dexcom G5®/Free Style Libre®	17/75

Data are presented as mean ± SD, or as numbers and percentages. CVD: Cardiovascular Disease, MDI: Multiple doses of insulin.

* Pre-lockdown period.

Regarding glucometric results, TIR 70–180 mg/dL, as well as, time > 180 mg/dL and > 250 mg/dL significantly improved in the lockdown period (Table 2). This significant improvement occurred while time < 70 mg/dL, < 54 mg/dL and glucose variability remained unchanged. A significant reduction of 0.2% points in GMI was observed. It is remarkable the high percentage of sensor use in both periods of time without any difference in number of scans performed per day (Table 2). No clinically significant differences were observed in either total insulin or skipped in basal/bolus dose per day (Total Daily Long-acting Insulin dose, 24.8 ± 8.5; Total Daily Rapid-acting Insulin dose, 26.2 ± 14.02 and Total Daily Insulin dose, 50.9 ± 18.8 units/day).

We evaluated the proportion of patients achieving consensus statement targets [11] in relation to sensor glucose values in both periods. Although there was a tendency to an improvement in all comparisons favoring the lockdown period, none of these differences were statistically significant (Table 3).

Considering a change in HbA_{1c} > 0.4% as clinically relevant, this difference was reached in 31.5% of the population during the lockdown (25% reached a decrease in GMI > 0.5%). A 45.7% of the population increased the TIR 70–180 mg/dL more than a 5% during the lockdown.

Finally, we performed the analysis of data for two groups: isCGM and rtCGM users. In the case of isCGM (n = 75) results did not change in comparison with the whole group and

results in glucometrics remained strictly the same. In the case of rtCGM group (n = 17), the improvement during lockdown became only apparent in time < 70 mg/dL (7.35 ± 5.31 vs 5.41 ± 4.12%; p < 0.05) and time < 54 mg/dL (2.00 ± 1.84 vs 1.47 ± 1.37%; p < 0.05).

4. Discussion

The use of standalone continuous glucose monitoring allows patients with T1D at high risk of hypoglycemia to manage glucose control even throughout the exceptional living conditions imposed by the strict lockdown due to COVID-19 pandemic crisis. Lockdown period was associated with some improvement in glucometric parameters especially those associated with glucose exposure.

The COVID-19 pandemic has forced the public authorities to impose extraordinary policies and restrictions to limit the virus spread. Lockdown has been recognized as an effective measure to reduce the risk of infection. The effect of this extreme and prolonged condition on glycemic control in people with T1D was totally unknown. There have been few reports describing the effects of this exceptional situation in glucose profile of T1D patients using standalone CGM, pumps or hybrid-closed-loop systems (HCL). In a group of adolescents with T1D treated with an HCL, Tornese et al. [12] showed that glucose control did not deteriorate due to restrictions due to COVID-19 and further improved in adolescents

Table 2 – Changes in CGM variables in pre-lockdown and within-lockdown.

	Pre-Lockdown	Within-Lockdown	p
Mean sensor glucose concentration (mg/dL)	160.8 ± 30.7	153.5 ± 27.0	0.001
GMI (%)	7.2 ± 0.8	7.0 ± 0.8	0.005
Coefficient of Variation (%)	37.9 ± 7.5	38.0 ± 6.8	n.s.
Time in Range 70–180 mg/dL (%)	59.3 ± 16.2	62.6 ± 15.2	0.002
Time > 180 mg/dL (%)	34.4 ± 18.0	30.7 ± 16.9	0.002
Time > 250 mg/dL (%)	11.1 ± 10.6	9.2 ± 9.7	0.02
Time < 70 mg/dL (%)	6.3 ± 4.8	6.4 ± 5.8	n.s.
Time < 54 mg/dL (%)	1.9 ± 2.6	1.8 ± 3.1	n.s.
Sensor use (%)	95.7 ± 8.3	95.1 ± 7.2	n.s.
Number of scans per day	12.4 ± 6.2	12.5 ± 6.6	n.s.

Data are presented as mean ± SD, or as numbers and percentages. GMI: glucose management indicator. n.s.: non-significant.

Table 3 – Proportion of patients achieving consensus statement targets in relation to sensor glucose values in both periods.

	Pre-Lockdown	Within-Lockdown	p
<1% of time <54 mg/dL	36 (39.1)	33 (35.9)	n.s.
<4% of time <70 mg/dL	33 (35.9)	37 (40.2)	n.s.
>70% of time 70–180 mg/dL	25 (27.2)	29 (31.5)	n.s.
<25% of time >180 mg/dL	28 (30.4)	36 (39.1)	n.s.
<5% of time >250 mg/dL	33 (35.9)	36 (39.1)	n.s.
<7% GMI	40 (43.5)	45 (48.9)	n.s.
<36% of CV	29 (31.5)	34 (37.0)	n.s.

Data are presented as numbers (percentages). n.s.: non-significant.

who continued physical activity in a safe home environment. Bonora et al. [13] reported data from 33 individuals with T1D who were monitoring their glucose levels using an intermittently scanned CGM. They demonstrated a beneficial effect of lockdown, mainly in TIR, and suggest that slowing down routine daily activities can have beneficial effects on T1D management. In the same way, and also in a general population of patients with T1D, Beato [14] recently described no deleterious effect of lockdown due to COVID-19 pandemic on glycemic control in adults with T1D using CGM, with an improvement in TIR.

In our study, we evaluated the impact of lockdown in a different and particularly vulnerable population. We included people with T1D prone to recurrent severe hypoglycemia. The use of standalone CGM has been significantly associated with a reduction in the frequency of non-severe and severe hypoglycemic events in hypoglycemia-prone adults compared with the use of self-monitoring-blood-glucose finger pricks [8,9]. In comparison with the population included in the manuscript by Beato [14], the percentage of time < 54 and < 70 mg/dL in our population is almost double before lockdown. Despite this, the percentage of TIR during the lockdown and the improvement observed in glucose exposure in our study was almost the same without any significant increase in hypoglycemia. Near the 40% of our patients reached <4% of time <70 mg/dL and half of them had a GMI < 7%. Thus, regular and homogeneous daily life conditions and activity in a safe home environment imposed by strict lockdown may contribute to facilitate glucose management also in a high-risk population with T1D. This includes increased consumption of homemade food facilitating carbohydrate counting and the administration of boluses at time, decreased workloads and increased time to cope with diabetes. Our results contrast with the estimation of the effects of lockdown due to COVID-19 in glycemic control published by Ghosal et al. [15]. In that study the authors estimated a worsening of glycemic control related to the duration of lockdown, as well as, an increase in the diabetic complication rates.

isCGM and rtCGM are different technologies with a different evidence based and clinical results. There are previous publications showing that rtCGM more effectively reduces time spent in hypoglycemia in people with T1D and impaired awareness of hypoglycemia compared with isCGM [9]. However, it is necessary to remark the small number of patients using rtCGM (n = 17) in our sample and that a selection bias to decide on to start rtCGM cannot be ruled out.

Our study has limitations. It is a retrospective, observational real-world condition study and due to this nature only an association between the CGM data obtained in both periods of time, and not causation, can be inferred from the results. We did not analysed changes in daily life and diabetes management that may influence the results in glucose control. The glucose profile information was obtained from two short periods of time and we do not know whether positive findings can be extended over a longer period of time. The population included in the study belongs to a single reference Diabetes Unit with a high expertise in the management of CGM. Thus, the findings could not be considered representative for populations from other centers.

We think that our study has also some strength. The exceptional, almost experimental, living conditions imposed by the very strict lockdown measures imposed in Spain gave to us the opportunity to test the effects of restrictive and homogenous lifestyle conditions staying at home on glycemic profile of patients with T1D. We could also evaluate the effectiveness of technology in a particular group of high-risk patients in such conditions. Finally, because we pre-planned the sample size of subjects in our study, we feel confident with the difference we found in TIR between both periods of time.

In summary, very restrictive lockdown conditions imposed by the COVID-19 pandemic may be managed successfully in terms of glycemic control by population with T1D prone to hypoglycemia using CGM. The strict daily routine at home could probably explain the improvement in the time in glycemic target without increasing the time hypoglycemia.

Declaration of Competing Interest

Dr Viñals has received lecturing fees from NovoNordisk A/S, Medtronic Inc., Sanofi-Aventis and MSD. Dr Giménez has received lecturing and consulting fees from Medtronic Inc., Eli Lilly & Co., NovoNordisk A/S, Sanofi-Aventis, Astra Zeneca and MSD. Dr Conget reported receiving lecturing and consulting fees from Medtronic Inc., Bayer AG, GlaxoSmithKline, Eli Lilly & Co., NovoNordisk A/S, Sanofi-Aventis, Novartis, Astra Zeneca and MSD.

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Author's contributions

CV, MG and IC contributed to the study concept, designed the study and provided statistical advice on study design. CV, IC had full access to all data in the study and takes responsibility for the integrity of data and accuracy of data analysis and wrote the article.

AM, DR, IP, MV collected and reviewed the data. All authors contributed to the interpretation of data and the drafting of the report. They critically revised the report for important intellectual content and approved the version to be published.

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