Original Research Paper

Reduction of hypoglycemia, lifestyle modifications and psychological distress during lockdown following SARS-CoV-2 outbreak in type 1 diabetic patients using flash continuous glucose monitoring: a retrospective cohort study

Running title: *Hypoglycemia during COVID-19 in T1D patients on FGM*

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Abstract word count: 224

Manuscript word count: 2796

Number of references: 25

Number of tables: 5

Abstract

Aims: To assess changes in glucose metrics and their association with psychological distress and lifestyle changes in patients with type 1 diabetes (T1D) using flash glucose monitoring (FGM) during lockdown following SARS-CoV-2 outbreak.

Materials and methods: Single-center, observational, retrospective study enrolling T1D patients who attended a remote visit on April 2020 at the Endocrinology division of the University Hospital Policlinico Consorziale, Bari, Italy. Lockdown-related changes in physical activity level and dietary habits were assessed on a semi-quantitative basis. Changes in general well-being were assessed by the General Health Questionnaire-12 items (GHQ-12) with a binary scoring system. Glucose metrics were obtained from the Libreview platform for the first two weeks of February 2020 (T0) and the last two weeks before the phone visit (T1).

Results: Out of 84 patients assessed for eligibility, 48 had sufficient FGM data to be included in the analysis. FGM data analysis revealed significant reductions in coefficient of variation (CV), number of hypoglycemic events and time below range (TBR), while no changes were found in time in range (TIR), time above range (TAR), mean sensor glucose (MSG) and glucose management indicator (GMI). Moreover, the frequency of sweets consumption was inversely related to the occurrence of hypoglycemic events during lockdown.

Conclusions: Lockdown-related lifestyle changes, albeit unhealthy, may lead to reduction in FGM-derived measures of hypoglycemia and glycemic variability in patients with T1D.

Keywords: COVID-19, FGM, hypoglycemia, lifestyle, lockdown, type 1 diabetes.

Introduction

At the beginning of 2020, the world was challenged by the fearsome outbreak of SARS-CoV-2 infection.[1] On March 9th, the Italian Government ordered a nationwide lockdown to reduce the rate of contagion and prevent the collapse of the national health care system.[1] People were not allowed to leave their houses except for urgent necessity, and all non-essential businesses were forced to close with employees being either put on furlough or home working.[2] The Italian National Institute of Health offered guidance on how to preserve general well-being through correct lifestyle[3] to limit the potential increase of quarantine-related unhealthy food consumption and reduction in physical activity. In addition, both the lockdown measures and spread of SARS-CoV-2 pandemic exerted an unfavorable psychological impact, as it was inferred from both Chinese[4] and European[5] studies showing somewhat increased prevalence of depression, anxiety and post-traumatic stress disorder (PTSD) in the general population. Both lifestyle and psychological issues have been deemed essential to diabetes care.[6] Therefore, in patients with diabetes, the harmful combination of quarantine-associated unhealthy habits, increased mental stress and suspension of non-urgent face-to-face visits due to social restrictions may potentially result in deterioration of glucose control and disease self-management.

Cloud-based platforms supporting diabetes data sharing from blood glucose meters and interstitial glucose monitors give physicians a chance to remotely follow their patients' glucose profiles and provide therapeutic suggestions.[7] Flash glucose monitoring (FGM) provides users with on-demand interstitial glucose readings, glucose trend information, and historical data to support effective diabetes self-management.[8–10] Glucose readings are stored every 15 minutes as long as a patient scans the sensor at least once every 8 hours, and can be accessed for retrospective analysis.[11] Recently, quarantine-associated abnormalities in glucose metrics have beeen retrospectively documented in patients with type 1 diabetes (T1D) wearing glucose sensors.[12–14] However, determinants of the observed modifications, including mental stress and changes in physical activity and dietary patterns, have not been investigated. In this study, we assessed lockdown-related changes in glucose control and variability and their association with psychological distress and lifestyle changes in T1D patients using the Freestyle Libre (Abbott Diabetes Care Inc., Alameda, CA, USA) FGM system.

Methods

This was a single-center, observational, retrospective study, conducted at the Endocrinology Division of the University Hospital Policlinico Consorziale, Bari, Italy. The study was carried out in adherence with Good Clinical Practice, ICH Harmonized Tripartite Guidelines for Good Clinical Practice and Declaration of Helsinki, and was approved by the local Institutional Ethics Committee (study no. 6375, approved on May 12, 2020). All patients attending our diabetes outpatient clinic who received a prescription for FGM underwent a remote visit on April 2020 were assessed for eligibility criteria and enrolled in the study with informed consent. Inclusion criteria were: both males and females; age ≥18 years; T1D for at least 1 year; being on an intensive insulin regimen (either multiple daily injections, MDI, or insulin-pump, CSII) for at least 6 months; using the FreeStyle Libre (Abbott Diabetes Care Inc.) FGM system for at least 3 months; having their glucose data uploaded to the Libreview platform (www.libreview.com). Major exclusion criteria were: history of acute myocardial infarction, stroke, percutaneous or surgical revascularization within the last 30 days; active neoplasia or history of chemotherapy- and/or radiation-treated neoplasia within the last 6 months; being pregnant in the last 3 months; any other concomitant medical or psychological condition which, in the judgment of the Investigator, made the patient unsuitable for study participation.

For each individual patient the following information was collected during the phone visit and confirmed in their clinical record: age, sex, last recorded BMI, education level, occupational status and change in working habits during the lockdown period, last HbA1c value, lifestyle changes during the lockdown period (specifically, change in physical activity and/or dietary habits), changes in general well-being as assessed by the General Health Questionnaire-12 items (GHQ-12). Changes in physical activity level and dietary habits were assessed on a semi-quantitative basis (higher/lower/same frequency) with an ad hoc questionnaire (Supplementary Appendix). The GHQ-12 is a self-administered screening tool for nonpsychotic mental disorders, in addition to representing a more general measure of psychiatric well-being (Supplementary Appendix).[15] When a binary scoring system (0-0-1-1) is used to rate the responses, the GHQ-12 may help identify minor psychiatric disorders within a community or non-psychiatric clinical settings, such as primary care or general medical outpatients, yielding final scores that range from 0 to 12. The GHQ-12 was already used to assess psychological distress after traumatic events or disease-related distress in people with diabetes and it is a reliable and sensitive tool to detect clinical changes.[16] In our study, patients scoring ≥4 were considered to be at risk for anxiety/depression (GHQ-positive).[17] Fourteen-day measures of glycemic control and variability, including 24-hour mean sensor glucose (MSG), glucose management indicator (GMI), coefficient of variation (CV), time spent in the 70-180 mg/dl glucose range (TIR), time spent in level 1 (<70-54 mg/dl) and level 2 (<54 mg/dl) hypoglycemia, time spent in level 1 (>180-250 mg/dl) and level 2 (>250 mg/dl) hyperglycemia, and number of low glucose (<70 mg/dl) events and their duration, were obtained from the Libreview platform for the following periods: (i.) the first two weeks of February 2020 (baseline or T0), before the first Italian COVID-19 patient was identified, and (ii.) the last two weeks before a scheduled phone visit (lockdown period or T1). Sensor data sufficiency and daily scan frequency were also obtained. The primary and secondary endpoints were evaluated in patients with ≥70% FGM data in both the baseline and lockdown period. The primary endpoint was change in the number of hypoglycemic events during lockdown. As secondary endpoints, changes in the following outcomes were evaluated: TIR, time spent above the 70-180 mg/dl glucose range (TAR), time spent below the 70-180 mg/dl glucose range (TBR), MSG, GMI, CV, and number of daily scans.

Statistical analysis

Normally distributed continuous variables are reported as mean ± standard deviation, non-normally distributed continuous variables as median [interquartile range] and categorical variables are presented as count (percentage). The D'Agostino & Pearson test was used to assess for data normality. A two-tailed paired Student's t-test was performed for normally distributed continuous variables, a Wilcoxon matched-pairs signed rank test was used for non-normally distributed continuous variables, and a chi-square test was run to test for differences in categorical variables in order to evaluate differences from T0 to T1. A two-tailed unpaired Student's t-test was performed for normally distributed variables and a Mann Whitney test was performed for non-normally distributed variables to investigate differences between the subgroup of patients experiencing less hypoglycemic events during lockdown compared to the subgroup of patients with an increased or unvaried number of hypoglycemic events. A multiple linear regression model was used to investigate the effect of patients' characteristics and lifestyle changes on the lockdown-associated difference in number of hypoglycemic events. The statistical analysis was performed using GraphPad Prism software (version 8.4.2 for macOS, GraphPad Software, La Jolla, CA, USA). A two-sided p-value <0.05 was regarded as statistically significant.

Results

A total of 84 patients regulalry attending our outpatients diabetes clinic and using FGM were assessed for eligibility: 54 met the inclusion criteria and were enrolled in the study; 3 patients were excluded due to pregnancy, 1 patient was excluded due to chemotherapy within the previous 6 months, 15 patients had T2D, 9 patients did not upload data to the Libreview platform, and 2 patients were not using FGM at the time of the remote visit. Only 48 had sufficient FGM data (>70%) to be included in the final analysis. For most patients (87.5%) the phone visit occurred between April 3 and April 11. There were no reported cases of SARS-CoV-2 infection among enrolled patients, nor hospitalizations for chetoacidosis or severe hypoglycemia.

Clinical features of included patients are listed in Table 1. During lockdown, 37.5% of patients reported small treatment modifications, which accounted for <10% of the total daily insulin dose, and 22.9% had consultation with a diabetologist.

As a result of lockdown restrictions, 23 patients (47.9%) had their working habits changed, of which 15 (31.2%) were placed on furlough and 8 (16.6%) switched to home working.

Mean GHQ-12 score was 4.5, with 50% of patients reporting a score above the ≥4 cut-off level, thus being at risk of mild psychological distress. Interestingly, the total GHQ-12 score did not differ accordingly to changes in working habits (p=0.77). Most patients (72.1%) reported that they did not change the number of meals per day, though 39.6% and 35.4% of patients increased the frequency of starchy foods and sweets consumption, respectively (Table 2). As expected, 64.6% of patients were less engaged in physical activity during the lockdown period than in the pre-COVID baseline time frame (Table 2).

FGM data sufficiency was high both at baseline and during lockdown (100% [95 – 100] and 100% [92 – 100], respectively). FGM data analysis revealed a significant reduction in CV, TBR and the number of hypoglycemic events, while no change was found in TIR, MSG and GMI (Table 3). Restricting the analysis only to the 37 patients who did not report a consultation with their diabetologist led to the same results (Supplementary Appendix). Morover, no differences in lockdown-related changes in FGM-derived glucose metrics were found between patients on MDI and on CSII, respectivey (Supplementary Appendix).

At T1 compared to T0, the number of hypoglycemic episodes decreased in 62.5%, increased in 31.3%, and exhibited no variation in 6.2% of the patients. Those patients who experienced a reduction in the number of hypoglycemic events also showed larger increases in MSG, GMI, TAR, as well as reductions in CV and TBR, when compared to patients who displayed increased or unvaried number of hypoglycemic events ($p<0.05$) (Table 4).

A multiple linear regression including age, gender, baseline mean sensor glucose, change in physical activity, change in dietary habits and change in working habits was performed (Table 5). Increased frequency of sweets consumption was inversely related to the occurrence of hypoglycemic events at T1 ($p=0.002$). This model found no significant association between change in the number of hypoglycemic events and change in working habits; nonetheless, patients who experienced a reduction in the number of hypoglycemic episodes after the lockdown became effective exhibited modifications of their working pattern more frequently as compared to those who did not (60% vs. 27.8%, $p=0.04$). However, more evidence is required to confirm this association due to the small number of patients enrolled in this study.

Discussion

This was a single-center, observational, retrospective study giving a snapshot view of lockdown-related changes in measures of glycemic control and variability and their association with changes in daily life and general well-being in a cohort of FGM users with T1D from a tertiary referral center in Southern Italy.

Since March 2020, the routine of most Italian people has changed due to the adoption of nationwide lockdown measures to contain the spread of SARS-CoV-2 infection. Indeed, both men and women were forced to interrupt their own businesses and social practices, and spent most of the time at home, with all fitness facilities closed and severe restrictions regarding even outdoor physical activity. Also, due to overwhelming fear and anxiety about health, food could appear as a suitable source of relief with possible increase in the number of meals and excessive hypercaloric food intake.[18] In patients with diabetes, the deleterious combination of unhealthy lifestyle behaviors and very limited access to outpatient clinics led to the expectation of deterioration of glycemic control.

In this study, we have observed a significant reduction of hypoglycemia (either expressed as TBR or number of total events) and glycemic variability in the total cohort, in the absence of modifications of TIR, MSG, GMI and TAR (Table 3). Hypoglycemia represents a major issue in treatment intensification and has a detrimental impact on patients' quality of life.[9] However, reduction of hypoglycemic events is not invariably associated with better glycemic control. Indeed, in the subgroup of patients with less hypoglycemic events, significantly augmented MSG, GMI and TAR were documented (Table 4). This finding leads to question whether the improvement in hypoglycemic events might be due to a worse daily management of diabetes. Also, the reduction of glycemic variability is clinically relevant, as a growing body of evidence suggests the association of increased glycemic variability with the development of macrovascular complications in diabetes.[19,20]

Bonora et al. found no lockdown-related worsening of 7-day FGM metrics in a cohort of 33 patients with T1D from the Padua district, with TIR and MSG being even improved in a subgroup of 20 patients who had stopped working.[12] Evidence from the literature suggests that a 14-day period with at least 70% of sensor wear adds confidence that the data are a reliable indicator of usual glucose patterns, particularly for mean glucose, TIR, and hyperglycemia measures.[21,22] Since in our cohort sensor wear averaged 96% in each 14-day period, longer follow-up and greater time coverage could potentially explain the different findings between the two studies.

In another study, Beato-Vibora found no deterioration of glucose control following lockdown in a cohort of 147 T1D subjects using CGM or FGM, with reduction of estimated HbA1c and time above 180 mg/dl and 250 mg/dl, increase in TIR, no changes in time spent in hypoglycemia, but in the absence of any information on quarantine-related lifestyle changes.[13] Maddaloni et al. found no significant changes in TBR and number of hypoglycemic events during lockdown in the total cohort, but reported a significant reduction of TBR in the subgroup of patients at increased risk of hypoglycemia at baseline, in the absence of data concerning lifestyle modifications and psychological distress.[23] In our cohort, reduction of hypoglycemic events at T1 was associated with reduced professional engagement and higher intake of sweets. Indeed, patients experiencing modifications of their working patterns were more represented among those displaying reduction in the number of hypoglycemic events compared to those who did not (60% vs. 27.8%, p=0.04). Furthermore, 35.4% of patients reported they were eating more sweets than the pre-lockdown period (Table 2), and a higher frequency of sweets intake was independently associated with reduction in hypoglycemic events (Table 5). It could be hypothesized that more time at home might have had detrimental effects on dietary habits, e.g. increased intake of sweets, thus exerting a negative impact on glycemic control yet preventing hypoglycemia. In this regard, a regional uniqueness of our population sample can not be excluded. It should be noted, however, that information on lifestyle modifications, other than change in working habits,[12] is not available for the cohorts of patients whose glycemic control has been evaluated during lockdown in other studies;[12,13] thus, differences in dietary habits, physical activity engagement, and psychological stress might at least partially explain these inconsistencies.

With regard to psychological well-being, half of patients reported a GHQ-12 score above the ≥4 "caseness" cutoff. This prevalence is similar to other cohorts of patients with chronic diseases. Indeed, out of 158 Italian patients with primary antibody deficiencies switched to remote assistance during the COVID-19 pandemic, the GHQ-12 assessment showed that 42.3% were at risk of anxiety/depression.[24] However, it should be noted that the GHQ-12 questionnaire lacks specific questions regarding the impact of SARS-CoV-2 outbreak on general health. Furthermore, the GHQ-12 score was not related to hypoglycemia occurrence in our analysis.

This study has some limitations. First of all, sample size is relatively small, and this could have prevented the detection of differences in time spent in the desired glucose range, as noted in other similar studies. The small sample size might also have not allowed the adequate statistical power to investigate the impact of reduced physical activity on FGM-derived glucose metrics. Indeed, Tornese et al. demonstrated that continuing regular physical activity during lockdown, even if just indoors, was crucial to achieving a satisfying TIR in T1D adolescents using hybrid closed loop.[14] Also, changes in dietary habits and physical activity were only assessed on a semiquantitative basis with a self-administered, non-validated questionnaire. However, in line with the results in our cohort, the EPICO study, conducted in a population of undergraduate Italian students, showed that lockdown was associated with decreased physical activity in approximately half of the sample.[25] Moreover, the exclusion of patients unable to upload data to the Libreview platform, possibily because less proficient in the use of technology, might have left out individuals possibly at higher risk of worse diabetes management and whose glycemic control during lockdown remains unexplored due to the unfeasibility of in-person visits. Finally, information on basal and bolus insulin doses was not available at both time points, and change in daily insulin requirements should be investigated in future studies. However, only 37.5% of patients made adjustements to their daily insulin regimen during lockdown (Table 1).

In summary, we found a reduction in FGM-derived measures of hypoglycemia and glycemic variability in patients with T1D, possibly as a result of lockdown-related prolonged exposure to unhealthy lifestyle but independently of psychological distress.

Acknowledgments

Authors' contributions

IC, SDM, LL and FGiorgino conceived and designed the study. IC and SDM wrote the manuscript. IC, SDM, FGiordano, FGuarini retrieved data. IC conducted statistical analysis. LL, SP, AL, AN, FGiorgino reviewed the manuscript. All authors have read and approved the final manuscript.

Conflict of Interest

IC, FGiordano, FGuarini, AL and SP have no competing interests. SDM has received speaker fees from Abbott and Roche Diabetes Care and has provided advisory services to Roche Diabetes Care. AC has received speaker fees from AstraZeneca, Eli Lilly, Novo Nordisk, Roche Diagnostics, Sanofi Aventis. AN has received speaker fees from AstraZeneca, Novo Nordisk and Sanofi Aventis. FG has received research support from Eli Lilly, Lifescan, Takeda, and has provided advisory services to AstraZeneca, Boehringer Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Novo Nordisk, Roche Diabetes Care, and Sanofi Aventis. LL has received speaker fees from Abbott, Astra Zeneca, Eli Lilly, Medtronic, Menarini, Novo Nordisk, Roche Diabetes Care, and Sanofi Aventis and has provided advisory services to Abbott, Astra Zeneca, Eli Lilly, Novo Nordisk, Roche Diabetes Care, Sanofi Aventis and Takeda.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethical approval

The study was approved by the local Institutional Ethics Committee (study no. 6375, approved on May 12, 2020) and carried out in adherence with Good Clinical Practice, ICH Harmonized Tripartite Guidelines for Good Clinical Practice and Declaration of Helsinki, and was. All individuals provided informed consent before enrolment.

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Table 1. Characteristics of study population.

N	48
Age (yrs)	42.4 + 15.9
BMI (kg/m^2)	23.5 ± 0.6
Female	23 (47.9)
Education level	
Elementary school degree	2 (4.2)
Middle school degree	6 (12.5)
High school degree	25 (52.1)
University degree	15 (31.2)
HbA1c (%)	7.4 + 1.0
Insulin therapy	
MDI	39 (81.5)
CSII	9 (18.7)
Working habits	
Unchanged (retired/unemployed/regular work)	25 (52.1)
Changed (on furlough/remote work)	23 (47.9)
Diabetologist consultation	11 (22.9)
Treatment modification	18 (37.5)

Data are expressed as mean + standard deviation or as counts (percentage).
MDI, multiple daily injections; CSII, continuous subcutaneous insulin infusion.

Table 2. Dietary habits and physical activity during lockdown (T1) compared to baseline (T0).

	Meals/day	Starchy foods	Sweets	Whole grains	Vegetables	Physical activity
Increased	11 (22.9)	19 (39.6)	17 (35.4)	7 (14.6)	12 (25.0)	9 (18.7)
Unchanged	35 (72.1)	19 (39.6)	23 (47.9)	24 (70.8)	27 (56.2)	8 (16.6)
Reduced	2 (4.2)	10 (20.8)	8 (16.6)	7 (14.6)	9 (18.7)	31 (64.6)

Data are expressed as counts (percentage).

Table 3. Changes from baseline of FGM-derived glucose metrics during lockdown.

	Baseline (T0)	**Lockdown (T1)**	**Difference (T1-T0)**	***p***
MSG (mg/dl)	157.6 ± 23.7	159.9 ± 26.9	2.3 ± 15.0	0.29
GMI (%)	7.1 ± 0.6	7.1 ± 0.6	0.06 ± 0.3	0.26
CV (%)	38.3 ± 7.4	35.1 ± 6.1	-3.1 ± 5.2	**0.0001**
TIR (%)	60.8 ± 14.1	60.8 ± 17.4	0.0 ± 9.7	0.9
TAR (%)	32.8 ± 14.6	34.6 ± 17.9	1.79 ± 9.8	0.21
TBR (%)	6.3 ± 5.5	4.5 ± 3.3	-1.8 ± 4.5	**0.008**
Hypoglycemic events (N)	10.0 [5.0– 17.0]	8.5 [6.0 – 13.0]	-2.0 [-5 – 0]	**0.0024**
Scans/day (N)	11.0 [8.8– 15.0]	13.0 [9.0– 17.0]	1.0 [-1.0 – 0]	0.28

Normally distributed data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median [interquartile range].
Differences between paired groups of normally distributed data have been assessed with Student's t-test, whereas differences between paired groups of non-normally distributed data have been assessed with the Mann-Whitney test.
MSG, mean sensor glucose; GMI, glucose management indicator; CV, coefficient of variation; TIR, time in range (70-180 mg/dl); TAR, time above target glucose range; TBR, time below target glucose range.
In bold, statistically significant p-values.

Table 4. Changes in FGM-derived glucose metrics during lockdown compared to baseline (T1-T0) in patients with reduced vs. increased number of hypoglycemic events.

Changes in FGM metrics (T1-T0)	**Patients with reduced hypoglycemic events (30)**	**Patients with increased/unvaried hypoglycemic events (18)**	***p***
MSG (mg/dl)	7.2 ± 14.0	-5.9 ± 13.0	**0.002**
GMI (%)	0.18 ± 0.34	-0.14 ± 0.3	**0.001**
CV ((%)	-4.5 ± 5.3	-0.84 ± 4.3	**0.01**
TIR (%)	-0.83 ± 10.0	1.4 ± 9.4	0.44
TAR (%)	4.3 ± 9.5	-2.3 ± 9.1	**0.02**
TBR (%)	-2.0 [-5.0 – -0.75]	0.5 [0.0 – 2.3]	**<0.0001**
Hypoglycemic events (N)	-6.0 [-10.0 – -2.8]	3.0 [1.0 – 4.0]	**<0.0001**

Normally distributed data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median [interquartile range].
Change in hypoglycemic events during lockdown was assessed as number of hypoglycemic events during lockdown (T1) minus number of hypoglycemic events at baseline (T0).
Differences between unpaired groups of normally distributed data have been assessed with Student's t-test, whereas differences between unpaired groups of non-normally distributed

data have been assessed with the Mann-Whitney test. In bold, statistically significant *p*-values.

MSG, mean sensor glucose; GMI, glucose management indicator; CV, coefficient of variation; TIR, time in range (70-180 mg/dl); TAR, time above target glucose range; TBR, time below target glucose range.

In bold, statistically significant *p*-values.

Table 5. Multiple linear regression model, adjusted for age, gender and baseline mean sensor glucose, predicting change from baseline (T1-T0) in the number of hypoglycemic episodes during lockdown.

Predictor	Estimated regression coefficient	SE	t Statistic	p-value	95% CI
Intercept	-19.81	6.61	2.99	**0.005**	-33.15, -6.47
Less physical activity	-1.98	1.91	1.03	0.31	-5.83, 1.88
More sweets	-6.86	2.12	2.07	**0.002**	-11.15, -2.59
Change in working habits	-1.22	0.04	0.72	0.47	-4.89, 2.32

Number of observations: 48, degrees of freedom 41

Multiple R: 0.5672, R-squared: 0.3217, Adjusted R-squared: 0.2224

F-statistic: 3.241 on 6 and 41 DF, p-value: 0.01

SE, standard error; CI, confidence interval; MDI, multiple daily injections.

In bold, statistically significant *p*-values.