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Effects of work status changes and perceived stress on glycaemic control in individuals with type 1 diabetes during COVID-19 lockdown in Italy



Ilaria Barchetta^{a,1}, Flavia Agata Cimini^{a,1}, Laura Bertocchini^{a,1}, Valentina Ceccarelli^a, Michele Spaccarotella^{b,c}, Marco Giorgio Baroni^{d,e}, Maria Gisella Cavallo^{a,*}

^a Department of Experimental Medicine, Sapienza University of Rome, Italy

^b Italian Institute of Scientific Sexology, Rome, Italy

^c Department of Biotechnological and Applied Clinical Sciences (DISCAB), University of L'Aquila, Italy

^d Department of Clinical Medicine, Public Health, Life and Environmental Sciences (MeSVA), University of L'Aquila, Italy

^e Neuroendocrinology and Metabolic Diseases, IRCCS Neuromed, Pozzilli (Is), Italy

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ABSTRACT

Aims: To evaluate the effects of COVID-19 lockdown on blood glucose control in individuals with type 1 diabetes (T1D) and to explore determinants of glucose variability.

Methods: Fifty T1D patients undergoing continuous/flash glucose monitoring were recruited. The study's primary outcome was the change of time in range (TIR) from before to lockdown period. Three time-point comparisons of TIR, mean glucose levels (MG), estimated (e)HbA1c, time above (TAR) and below range (TBR), moderate/severe hypoglycemic events between pre-lockdown, lockdown and post-lockdown period were also performed. Information on lockdown-associated perceived stress, changes of work status and physical activity were recorded.

Results: TIR significantly decreased (75(63–84)% vs. 69(50–76)%, $p < 0.001$) whereas MG (154 ± 15 mg/dl vs. 165 ± 25 mg/dl, $p = 0.027$) and eHbA1c (7.3(6.6–7.8)% vs. 7.5(6.7–8.2)%, $p = 0.031$) increased from pre- to lockdown period; overall glucose control significantly improved when restriction ended. Lockdown-associated work loss/suspension independently predicted impaired TIR after adjustment for potential confounders (Standardized β : -0.29 ; 95%CI: -18.7 to -2.25 ; $p = 0.01$). Greater TAR, TBR and hypoglycemic events were also reported during the lockdown.

Conclusion: In T1D Italian individuals, blood glucose control significantly worsened during the COVID-19 lockdown; work instability and related issues represented the main determinant of impaired glucose variability in this population.

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* Corresponding author at: Department of Experimental Medicine, Sapienza University, Viale Regina Elena, 324, 00161 Rome, Italy. E-mail address: gisella.cavallo@uniroma1.it (M.G. Cavallo).

¹ IB, FAC, LB contributed equally to this article and share co-first authorship.

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1. Introduction

Italy has been the first Western country to be massively hit by the SARS-CoV-2 coronavirus epidemic. In late February 2020, the Italian Government enforced extraordinary and drastic public health measures in order to limit the spread of SARS-CoV-2 coronavirus disease (COVID-19) culminated in a complete lockdown of the Country between March and May 2020. Lockdown policies force a distortion in people daily routine, increasing sedentary behavior, changing eating patterns and exposing to psychological burden. Prolonged restrictions and massive lifestyle changes can affect frail individuals and those with chronic diseases, such as people with type 1 diabetes (T1D) [1,2]. Individuals treated with intensive insulin therapy are confronted several time per day with the complex task of achieving glycaemic targets by controlling food intake and meal components, insulin doses and exercise. Also, blood glucose is largely influenced by variables which are hardly predictable and which poorly respond to standard interventions, such as stress conditions, psychological issues, socio-economic disadvantage [3].

In this study, we aimed to investigate the effects of the COVID-19 lockdown on glycemic control in T1D subjects and to explore determinants of changes of glucose variability, particularly referring to the work status modification and perceived stress, as a consequence of the lockdown restrictions.

2. Material and methods

We recruited fifty consecutive patients with T1D treated by multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) plus continuous glucose monitoring (CGM) or flash glucose monitoring (FGM)

systems, referring to Diabetes outpatient clinics at Sapienza University, Rome, Italy. Participants gave their consent to use the sensor-derived glucose data for research purposes. Baseline clinical and metabolic parameters of our study participants are reported in Table 1.

The study's primary outcome was the change of blood glucose (BG) time in range (TIR; 70–180 mg/dl, %) [4] from pre-lockdown to lockdown period. Change of mean blood glucose levels (MG; mg/dl) and estimated glycosylated hemoglobin (eHbA1c; %, mmol/mol) in this timeframe was also evaluated. Secondary outcome measures were: changes of time below range (TBR; BG < 70 mg/dl, %) and time above range (TAR; BG > 180 mg/dl, %) from pre- to lockdown, median (IQR) number of moderate (BG: 70 to 50 mg/dl) and severe (BG < 50 mg/dl) hypoglycemic events. All the indicators of glucose control were re-evaluated after the lockdown ended and compared to those recorded during the pre-lockdown and lockdown period.

Sensor-derived data were collected during the same time intervals in all the study participants.

As a pre-lockdown period, we considered a two-week timeframe (20 January-3 February) preceding the beginning of COVID-19 associated restrictions (started on 9 March; ended on 4 May); for the lockdown, the interval between 28 March and 11 April and for the post-lockdown data recorded between 30 May and 13 June.

In all the study participants, we collected data on physical examination (height, weight, body mass index (BMI), waist circumference), metabolic profile, diabetes' duration, age at T1D onset, C-peptide, diabetes' complications and comorbidities and insulin requirement.

Data on the amount of physical activity, expressed as more or less than 3.5 h of exercise per week, were collected in the pre-lockdown and lockdown period.

Table 1 – Pre-lockdown clinical and metabolic characteristics of study participants. Data are shown as mean \pm SD or median value, as appropriate.

Age (years)	40.7 \pm 13.5
Sex (M/F; number of patients)	31/19
T1D duration (years)	17.7 \pm 9.7
Body Mass Index (BMI; kg/m ²)	24 \pm 3.1
Waist Circumference (cm)	88 \pm 14.7
Systolic Blood Pressure (SBP, mmHg)	124.2 \pm 11.1
Diastolic Blood Pressure (DBP, mmHg)	77.6 \pm 9.4
Fasting blood glucose (FBG, mg/dl)	157.2 \pm 61.7
HbA1c (%; mmol/mol)	7.3(6.6–7.8), 56(49–62)
Serum creatinine (mg/dl)	0.78 \pm 0.17
Total Cholesterol (mg/dl)	183.3 \pm 37.6
HDL Cholesterol (mg/dl)	61.6 \pm 16.7
LDL Cholesterol (mg/dl)	104.3 \pm 30.6
Triglycerides (mg/dl)	84.3 \pm 38.7
C-peptide (ng/ml)	0.25 \pm 0.24
MDI/CSII (number of patients)	28/22
Guardian/Dexcom/Eversense/FreeStyleLibre (number of patients)	7/12/3/28
Physical activity (>3.5 h/week yes/no; number of patients)	26/24

Information on work status at the baseline and changes due to the COVID-19 restrictions were recorded and tabulated as: i) loss of job, ii) suspension, iii) smart-working, iii) no change.

Perceived stress associated to the lockdown period was quantified through a validated questionnaire (PSS, perceived stress scale) measuring the degree to which situations in life are appraised as stressful [5]. The PSS was completed by all the participants when the restrictions ended. Individual PSS scores range from 0 to 40 with higher scores indicating higher perceived stress and are grouped in three categories: scores ranging from 0 to 13 indicate low stress, from 14 to 26 moderate stress and from 27 to 40 high perceived stress.

Data on lifestyle and changes associated to COVID-19 restrictions are shown in Table 2.

Since COVID-19 restrictions also applied to routine medical practice, all patients were followed up by teleconsulting, except for emergencies; they all had full access to diabetes medicaments and BG monitoring devices throughout the lockdown duration.

Statistics

SPSS version 25 was used to perform all the statistical analyses. Based on the sample size calculation, our study was powered 0.90 with a level of significance of 1% (two sided) [6].

Continuous variables are reported as the mean \pm standard deviation (SD) or median (interquartile range, IQR) and categorical variables as percentages. Comparisons between two paired groups were performed by Wilcoxon paired-test and 3 time-point comparisons by Friedman test. Correlations between parameters were explored by Spearman's bivariate analysis and sex-, age-controlled partial correlation analysis. The association between perceived stress and hypoglycemic events, we performed bivariate Spearman's correlation analyses considering the PSS score, the number of moderate and severe hypoglycemic events, along with the number of insulin bolus/day and units/day, as continuous variables. The relationship between higher PSS score and greater frequency of severe hypos persisted statistically significant at the age-, sex-controlled partial correlation analysis.

Finally, parameters independently associated to changes of TIR from pre- to lockdown period were identified by multivariate regression models including sex and age and variables correlated to TIR at the bivariate correlation analyses. Two-sided p -value < 0.05 was considered statistically significant, with a confidence interval of 95%

3. Results and discussion

In our study population, median TIR significantly decreased between pre- and lockdown period (median (IQR) %: 75 (63–84) % vs. 69 (50–76) %, $p < 0.001$) whereas MG levels

and eHbA1c significantly increased (MG: 154 ± 15 mg/dl vs. 165 ± 25 mg/dl, $p = 0.027$; median (IQR) eHbA1c: 7.3 (6.6–7.8) % vs. 7.5 (6.7–8.2) %, $p = 0.031$) (Table 1c). The percentage of patients in good glycaemic control -as indicated by TIR $> 70\%$ - fell from 60% to 42% ($p = 0.008$).

TIR reduction during the lockdown period was associated with increased number of severe hypoglycaemic events ($r = -0.39$, $p = 0.011$) and higher TAR ($r = -0.34$, $p = 0.025$).

No relationship was found between pre-to-lockdown TIR change and modification of time spent in physical activity.

Significantly increased TAR and TBR, as well as higher number of moderate and severe hypoglycaemic events between pre and lockdown period were also reported (Table 3).

TIR during the lockdown positively correlated with age ($r = 0.32$, $p = 0.03$) and pre-lockdown TIR ($r = 0.63$, $p < 0.001$) and inversely with pre-lockdown eHbA1c ($r = -0.37$, $p = 0.015$).

The lockdown median (range) TIR value was 66.5 (50–77) % in patients who continued working and 59.9 (41–71) % in those who experienced job loss/suspension. Lockdown TIR significantly declined in individuals who experienced job loss/suspension ($n = 16$; mean (IQR) TIR change from pre- to lockdown: -20.5 ($-27 - 0.25$) % in comparison to those who continued working (traditional/smart-working; $n = 34$; mean (IQR) TIR change from pre- to lockdown: -5.5 ($-13 - -1$) %; $p = 0.05$).

COVID-19 pandemic-associated work issue was the main determinant of reduced lockdown TIR in T1D individuals after adjusting for pre-lockdown TIR, sex, age, BMI and physical exercise (R of the model = 0.78; Standardized β – coefficient = -0.29 ; 95%CI: -18.7 to -2.25 ; $p = 0.013$).

As a consequence of the lockdown period, 14% people experienced severe and 61% moderate perceived stress; at the bivariate correlation analysis, T1D patients with higher perceived stress had greater frequency of severe hypoglycaemia ($r = 0.45$, $p = 0.003$) despite significantly lower number of insulin bolus and units administered per day in the post lockdown period ($r = -0.39$, $p = 0.014$; $r = -0.33$, $p = 0.04$, respectively). The relationship between higher PSS score and greater frequency of severe hypoglycemic events persisted statistically significant at the age-, sex-controlled partial correlation analysis ($r = 0.46$, $p = 0.002$).

The 3 time-point analysis showed significant changes of TIR ($p < 0.001$), MG ($p = 0.024$) and eHbA1c ($p = 0.017$) from baseline to lockdown and post-lockdown period. TIR, MG levels and eHbA1c significantly improved from the lockdown from the post-lockdown period (Table 1c).

The main result of this study is the detection of a significant worsening of glycaemic control in T1D individuals in previous good glycaemic control during COVID-19 lockdown, followed by a significant improvement when restriction ended. In our population, the major determinant of increased glucose variability was represented by the occurrence of work

Table 2 – Lifestyle of T1D patients during the lockdown period.

Work status (Job loss/Job suspension/Traditional work/Smart-working; number of patients)	4/12/24/10
Physical activity (>3.5 h/week) yes/no; number of patients)	20/30
Perceived stress (no-mild/moderate/severe; number of patients)	13/30/7

Table 3 – Indicators of glycaemic control in pre-lockdown, lockdown and post-lockdown. Wilcoxon paired-test applied: comparison between *pre- and lockdown, °lockdown and post-lockdown. ^ Repeated measures Friedman test. Data are shown as mean ± SD or median (IQR) value, as appropriate.

Indicators of glycaemic control	Pre-lockdown	Lockdown	Post-lockdown	p-value
Mean glucose ± SD (mg/dl)	154 ± 15	165 ± 25	152 ± 20	0.027*; 0.05°; 0.024^
Estimated HbA1c %, mmol/mol	7.3(6.6–7.8)	7.5(6.7–8.2)	7.3(6.8–7.7)	0.031*; 0.026°; 0.017^
TIR (median (IQR), %)	56 (49–62)	58 (50–66)	56 (51–61)	<0.001*; <0.001°, <0.001^
TBR (median (IQR), %)	75 (63–84)	69 (50–76)	71(55–78)	<0.001*; <0.001°, <0.001^
TAR (median (IQR), %)	6 (2–13)	10 (3–17.5)	8.5 (3–15)	0.02*; 0.02°
Moderate hypoglycaemic events; number (range)	19 (7–31)	20(13–34)	19 (13–33)	0.07*; 0.05°
Severe hypoglycaemic events; number (range)	5 (3–8)	7 (2–12)	6 (2–10)	0.008*; 0.06°
	0.5 (0–2.75)	1 (0–7.5)	0 (0–2)	0.001*; 0.035°

instability and related issues. Indeed, perceived stress associated with the COVID-19 pandemic translated into glucose instability in the period following the lockdown, potentially indicating a dysfunctional adaptive reaction to lockdown-induced stress.

Other studies investigated changes of glucose control in relation to COVID-19 lockdown in children [7] and adults [8–12] with T1D, overall finding either comparable [7,12] or improved [8–11] glucose variability in these populations. However, unlike other study cohorts, our patients had pre-lockdown TIR above the optimal range (TIR > 70%). Moreover, in our study, time intervals for the data analysis were chosen in order to avoid that potential confounding factors related to the time of data collection could attenuate the specific impact of COVID-19 restrictions on glucose control. Indeed, as a pre-lockdown, we considered a time interval preceding the spread of the COVID-19 alert in Italy by mass media and for the lockdown, we selected the central period of the pandemic in Italy instead of the period immediately after the restrictions started [7,8,12]. Finally, unlike other investigations, we also analyzed glucose variability after almost one month from the end of the restrictions, the post-lockdown period.

Principal strengths of our study are: the recruitment of a homogeneous cohort of individuals all affected by T1D in good glycemic control before the lockdown, a 3-point collection of sensor-derived glucose data recorded in the same time interval in all the study participants, the evaluation of perceived stress through a validate scale, along with the collection of detailed information on work status changes as a consequence of the COVID-19 lockdown.

4. Conclusion

In Italian adults with T1D, blood glucose control significantly worsened as a consequence of the COVID-19 lockdown. Socio-economic issues and psychological burden display detrimental effects on glucose variability even in patients with T1D treated with standard of care therapies and previously in good metabolic control.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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