ORIGINAL RESEARCH

Glycaemic Control Among People with Type 1 Diabetes During Lockdown for the SARS-CoV-2 Outbreak in Italy

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ABSTRACT

Introduction: In late February 2020, due to the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the Italian Government closed down all educational and sport activities. In March, it introduced further measures to stop the spread of coronavirus disease (COVID-19), placing the country in a state of almost complete lockdown. We report the impact of these restrictions on glucose control among people with type 1 diabetes (T1D).
Methods: Data were collected on 33 individuals with T1D who were monitoring their glucose levels using a flash glucose monitoring device and remotely connected to the diabetes clinic on a cloud platform. We retrieved information on average glucose, standard deviation and percentage time in hypoglycaemia (< 70 mg/dl), glucose range (70–180 mg/dl) and hyperglycaemia (> 180 mg/dl). We compared glycaemic measures collected during lockdown to those collected before the SARS-CoV-2 epidemic and to the periods immediately before lockdown.
Results: In 20 patients who had stopped working and were at home as a result of the lockdown, overall glycaemic control improved during the first 7 days of the lockdown as compared to the weeks before the spread of SARS-CoV-2. Average glucose declined from 177 ± 45 mg/dl (week before lockdown) to 160 ± 40 mg/dl (lockdown; $p = 0.005$) and the standard deviation improved significantly. Time in range increased from 54.4 to 65.2% ($p = 0.010$), and time in hyperglycaemia decreased from 42.3 to 31.6% ($p = 0.016$). The number of scans per day remained unchanged. In 13 patients who continued working, none of the measures of glycaemic control changed during lockdown.
Conclusion: Despite the limited possibility to exercise and the incumbent psychologic stress, glycaemic control improved in patients with T1D who stopped working during the lockdown, suggesting that slowing down routine daily activities can have beneficial effects on T1D management, at least in the short term.

Keywords: COVID-19; Education; Epidemic; Sensor; Telemedicine

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Key Summary Points

Why carry out this study?

In March 2020, Italy was placed under lockdown due to the outbreak of the new coronavirus disease.

Diabetes management during lockdown was particularly challenging.

Using data collected by remote monitoring of glucose sensors, we investigated whether glycaemic control in people with type 1 diabetes (T1D) during lockdown improved or worsened.

What was learned from the study?

Individuals with T1D who stopped working during lockdown significantly improved their glucose control while those who continued working (essential services) showed no change in glucose control.

These results suggest that slowing down routine daily activities can achieve beneficial effects on the short-term management of T1D.

The long-term effects of lockdown and the factors that affect glucose control in this particular situation deserve future investigation.

INTRODUCTION

Achieving glycaemic control is a complex task for people with type 1 diabetes (T1D) as it involves multiple domains of daily functioning [1, 2]. To maintain glucose levels that are as much as possible within range, patients need to pay attention to meals, insulin doses, exercise regimens, working activities, social relations and psychological stress, as well as exercise self-control [3]. This continuous challenge results in people with T1D occasionally deprioritizing glycaemic control in favour of other activities [4]. Glucose control may improve during holidays, but this improvement is highly variable [5–7].

In December 2019, a new coronavirus (CoV) strain that causes severe acute respiratory syndrome emerged in Wuhan (China), ultimately referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and rapidly spread throughout the world [8]. In February and March 2020, Italy was the second most affected country worldwide [9]. To reduce the spread of infection, in late February 2020, the Italian Government issued a series of restrictions that, in March 2020, culminated in an almost complete lockdown of the country [10]. This lockdown intially involved all sport and educational activities but was then extended to commercial activities and most non-essential services. During lockdown, all citizens were requested to "stay at home" [11]. Outpatient clinics were closed while hospitals were coping with thousands of patients infected with SARS-CoV-2. The SARS-CoV-2 pandemic not only caused morbidity and mortality among people with CoV disease but also imposed a heavy burden on societal and population health [12]. It is expected that individuals with chronic disease, such as diabetes, will suffer the most from the prolonged lockdown due to limitations in access to outpatient clinics and services.

Remote glycaemic monitoring through cloud platforms has enabled diabetes specialists to interact with individuals with T1D during the SARS-CoV-2 pandemic lockdown. The widespread use of the flash glucose monitoring system (FGM) among patients with T1D [13] has allowed healthcare professionals (HCPs) to monitor these patients through a web-based interface that records real-time sensor readings. Of note, telemedicine has been shown to improve psychosocial outcomes in young adults with diabetes [14]. According to a recent meta-analysis, FGM has the potential to improve overall glucose control [15] and to reduce hypoglycaemia in individuals with T1D [16, 17].

In this study, we examined glycaemic control during the first week of lockdown against the spread of SARS-CoV-2 in people with T1D

using FGM in Italy in comparison to the pre-lockdown period.

METHODS

The study was approved by the Ethical Committee of the University Hospital of Padova. All procedures were performed in accordance with the Helsinki Declaration of 1964, and its later amendments, and was in agreement with national regulations. The study was conceived as a retrospective data collection, and all patients provided written informed consent to the reuse of clinical data for research purposes.

Study Design and Participants

Patients with T1D who were eligible for inclusion in the study met the following criteria: attended the diabetes outpatient clinic of the University Hospital of Padova; lived in the area; were using the FreeStyle Libre FGM system (Abbott Diabetes Care, Rome, Italy) for at least 3 months; were sharing sensor data with the diabetes outpatient clinic on a web-based cloud system (LibreView; Abbott Diabetes Care); and had > 90% coverage of sensor data. The Libre-View platform is intended to assist both people with diabetes and HCPs in reviewing, analysing and evaluating sensor data to support diabetes management. In order to record only spontaneous changes in glycaemic control, patients who had already sought therapeutic advice were excluded from enrolment. Patients had provided online informed consent to be remotely connected to the diabetes clinic.

Clinical Variables

Diagnosis of T1D was based on the American Diabetes Association (ADA) criteria and was confirmed by positive autoantibody testing [18].

For all patients, we retrieved the following data: age, sex, diabetes duration, body mass index, history of hypertension and smoking habit, most recent glycated haemoglobin (HbA1c) values, lipid profile, urinary albumin excretion rate (UAER), estimated glomerular filtration rate (eGFR; CKD-EPI equation [19]).

The presence of chronic complications was recorded as follows. Nephropathy was defined as a UAER > 30 mg/g or eGFR < 60 ml/min/1.73 m^2. Somatic neuropathy was defined based on an assessment using the Michigan Neuropathy Screening Instrument, and eventually confirmed by nerve conduction velocity testing. Autonomic neuropathy was defined based on the results of cardiac autonomic tests performed with the Neurotester instrument (Meteda Srl, San Benedetto del Tronto, Italy), including lying-to-standing response, Valsalva manoeuvre, deep breathing and orthostatic hypotension. Retinopathy (any stage) was defined based on the analysis of digital retinography, as scored by expert ophthalmologists. Coronary artery disease was defined as a history of myocardial infarction or coronary revascularization, or evidence of myocardial ischemia upon stress test (when available). Peripheral arterial disease was defined as a history of claudication or rest pain, peripheral artery revascularization or an ankle-brachial index of < 0.9. Cerebrovascular disease was defined as a history of stroke or transient ischemic attack or carotid atherosclerosis (symptomatic or asymptomatic). We also collected information on concomitant medications, other than insulin, including metformin, sodium glucose cotransporter-2 inhibitors and drugs for the management of concomitant risk factors.

Sensor Data and Definition of Periods

Raw data on sensor glucose readings were retrospectively retrieved from all patients at 15-min intervals. To avoid an impact of scan frequency on average glucose levels, we did not consider glucose readings from sensor scans in our analysis. Raw data were imported on a dedicated spreadsheet, and the following metrics were computed: average glucose with standard deviation (SD); coefficient of variation (CV%; expressed as the percentage of average glucose); time in hypoglycaemia (< 70 mg/dl); time in glucose range (70–180 mg/dl); time in hyperglycaemia (> 180 mg/dl); and number of
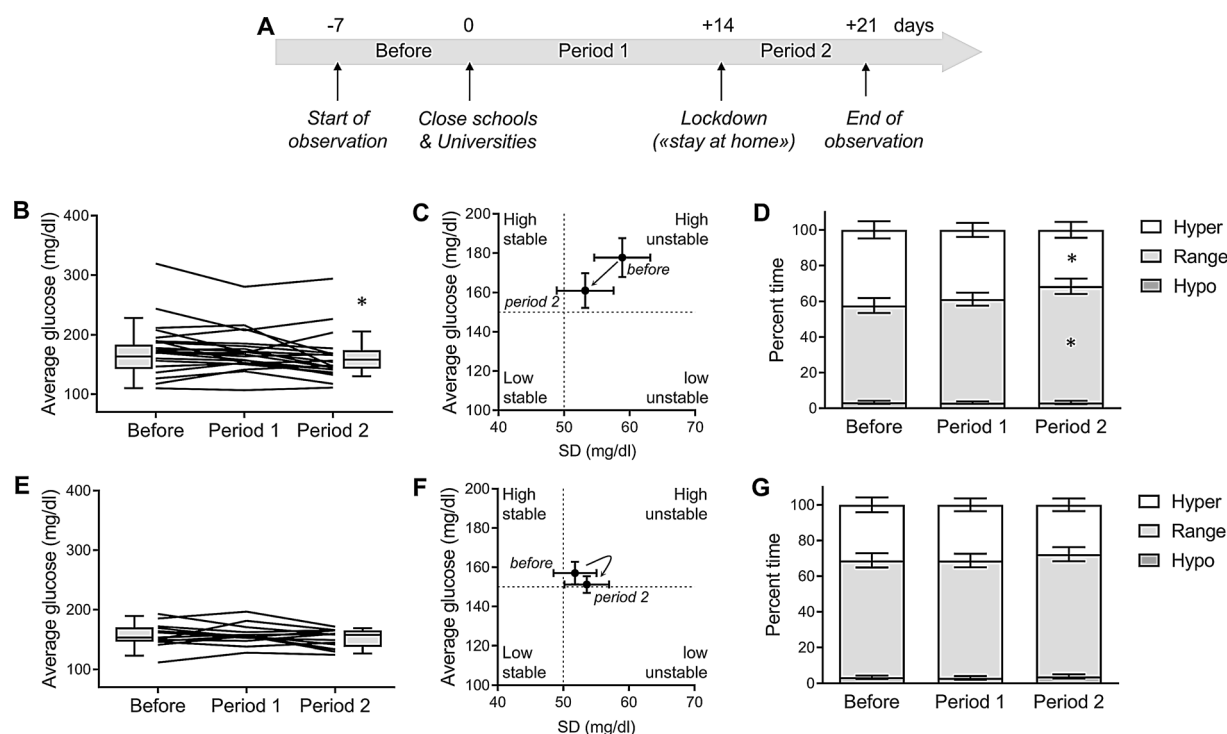
Fig. 1 Changes in glucose control parameters during lockdown. **a** Timeline of restriction measures. 'Before' refers to 1 week before the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in Italy; 'Period 1' refers to the time from the closure of all sport and educational activities to lockdown of the Padova area; 'Period 2' refers to the first week after lockdown. Panels **b–d** refer to patients who stayed at home (i.e. stopped working); panels **e–g** refer to patients who continued working. **b, e** Box and whisker plots showing changes in average glucose levels of individual patients (lines), with the horizontal line in box indicating the median, the top and bottom of the box indicating the upper and lower quartiles, respectively, and the whiskers indicating range/variability. **c, f** Change in the two groups of patients in terms of average glucose versus standard deviation (SD) plot. As per convention, cutoffs (dotted lines) are drawn at an average glucose of 150 mg/dl and a SD of 50 mg/dl to define high/low and stable/unstable control, respectively. **d, g** Percentage time in hypoglycaemia (Hypo; < 70 mg/dl), range (70–180 mg/dl) and hyperglycaemia (Hyper; > 180 mg/dl) in each group. Asterisk (*) indicates significant difference at $p < 0.05$ between period 2 and before the outbreak.

scans per day. As per convention, we set a cutoff of 150 mg/dl to define high/low average glucose and a SD cutoff of 50 mg/dl to define stable/unstable control. The primary endpoint was average glucose. These variables were calculated for each of the following periods (Fig. 1a): 3 months before the SARS-CoV-2 outbreak in Italy; 1 week before the SARS-CoV-2 outbreak in Italy; from the closure of sport and educational activities to lockdown of the Padova area, when commercial activities and non-essential services were closed (period 1); and the first week after lockdown (period 2).

Patients were divided into groups based on whether they stopped their working activities during lockdown or whether they continued working during lockdown because of being involved in essential services (e.g. workers in the healthcare system or food supply chain). Patients who continued working served as negative controls for those who stopped working during the lockdown period.

Statistical Analysis

Continuous variables are presented as the mean ± SD if normally distributed or as the median

Table 1 Baseline characteristic of patients with diabetes type 1 in the study

Variable	Stayed at home (stopped working)	Continued working
Number of patients	20	13
Age (years)	36.9 ± 13.4	45.0 ± 12.0
Sex male	12 (60.0%)	7 (53.8%)
Body mass index (kg/m^2)	24.0 ± 3.0	25.2 ± 2.3
HbA1c (%)	7.6 ± 1.2	7.3 ± 0.6
Diabetes duration (years)	15.0 ± 11.1	24.6 ± 12.3*
Concomitant risk factors		
Hypertension	3 (15.0%)	3 (23.0%)
Smoking	2 (10.0%)	1 (7.7%)
Total cholesterol (mg/dl)	181.7 ± 31.1	176.2 ± 19.7
HDL-cholesterol (mg/dl)	64.6 ± 21.3	63.0 ± 12.1
LDL-cholesterol (mg/dl)	98.3 ± 20.5	99.1 ± 5.3
Triglycerides (mg/dl)	94.0 ± 38.8	80.6 ± 9.1
Complications		
Nephropathy	3 (15.0%)	0 (0.0%)
Urinary albumin/creatinine ratio (mg/g)	7.0 [4.0–7.7]	4.0 [2.3–4.5]
eGFR (ml/min/1.73 m^2)	107.6 ± 21.0	97.1 ± 16.3
Neuropathy	2 (10.0%)	2 (15.3%)
Retinopathy	4 (20.0%)	4 (30.7%)
Coronary artery disease	0 (0.0%)	0 (0.0%)
Peripheral arterial disease	1 (5.0%)	0 (0.0%)
Cerebrovascular disease	3 (15.0%)	0 (0.0%)
Medications		
MDI/CSII	20/0	8/5*
Metformin	3 (15.0%)	1 (7.7%)
SGLT2i	3 (15.0%)	0 (0.0%)
ACEi/ARB	3 (15.0%)	3 (23.1%)
Other anti-hypertensive	1 (5.0%)	1 (7.7%)
Statins	4 (20.0%)	4 (30.8%)

Table 1 continued

Variable	Stayed at home (stopped working)	Continued working
Anti-platelet	3 (15.0%)	1 (7.7%)

Data are expressed as mean $\pm$ standard deviation or as the number (of patients) with the percentage in parenthesis. The urinary albumin creatinine ratio is expressed as the median with the interquartile range in square brackets

*Significant different between patient groups at $p < 0.05$

HDL High-density lipoprotein, *LDL* low-density lipoprotein, *MDI* multidose insulin, *CSII* continuous subcutaneous insulin infusion, *SGLT-2i* sodium glucose cotransporter-2 inhibitor, *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blockers

and interquartile range (IQR) if non-normally distributed. Normality was checked using the Shapiro–Wilk test, and non-normal variables were log-transformed before being analysed with parametric tests. Categorical variables were presented as percentages. Comparisons between two or more groups were performed using the two-tail unpaired Student's t test for continuous variables or the Chi-square test for categorical variables. Comparison of variables recorded before and after lockdown was performed using the two-tail paired Student's t test. The Wilcoxon rank test was used to compare paired categorical data. Statistical significance was accepted at $p < 0.05$.

RESULTS

A total of 33 patients with T1D were enrolled in the study, then categorized into one of two groups based on whether they stopped working ($n = 20$) or continued working ($n = 13$) during the lockdown. Clinical characteristics of the two groups are reported in Table 1. None of the patients were known to be (have been) infected with SARS-CoV-2 nor to be (have been) quarantined for close contact with infected people.

The 20 patients who stopped working due to the lockdown had an average age of 36.9 years, 60% were male and average diabetes duration was 15 years. The mean latest available HbA1c value was 7.6%, and the prevalence of complications was low. When data collected during the week before the SARS-CoV-2 outbreak in Italy were compared to those of the first week of lockdown (period 2), average glucose had

decreased from 177.7 $\pm$ 45.6 mg/dl (9.9 $\pm$ 2.5 mmol/l) to 161.0 $\pm$ 40.3 mg/dl (8.9 $\pm$ 2.2 mmol/l; $p = 0.005$; Fig. 1b), which is equal to a reduction of 16.7 $\pm$ 24.5 mg/dl (0.9 $\pm$ 1.4 mmol/l). The standard deviation of sensor readings decreased from 58.9 $\pm$ 19.6 mg/dl (3.3 $\pm$ 1.1 mmol/l) to 53.2 $\pm$ 19.9 mg/dl (3.0 $\pm$ 1.1 mmol/l; $p = 0.004$). As a result of the simultaneous improvement in average glucose and the standard deviation, patients moved from a high-unstable profile towards a low-stable profile (Fig. 1c). The number of patients in the low-stable profile area increased from three to eight ($p = 0.02$). However, the CV%, which is a better measure of glycaemic stability according to international consensus and recommendations [20, 21], did not change substantially across the periods considered.

Time in hypoglycaemia was not significantly changed, whereas time in range increased (from 54.4 $\pm$ 4.2 to 65.2 $\pm$ 4.2%; $p = 0.010$) and time in hyperglycaemia decreased (from 42.3 $\pm$ 4.8 to 31.6 $\pm$ 4.4%; $p = 0.016$; Fig. 1d). The number of scans per day did not change significantly (from 12.6 $\pm$ 2.4 to 13.4 $\pm$ 2.9; $p = 0.479$). Reduction of average glucose was directly correlated with baseline average glucose ($r = 0.47$; $p = 0.016$), but not with the number of scans per day.

When data collected during period 2 were compared to those collected during the 3 months before SARS-CoV-2 spread, the same significant improvements were noted (Table 2). Data collected during period 1 were not significantly different from those collected 1 week or 3 months before SARS-CoV-2 outbreak.

Table 2 Glucose control parameters in patients who stayed at home (not working) or continued to work during the lockdown in Italy

Variable	Patients who stayed at home (not working)				Patients who continued working			
	3 months before the SARS-CoV-2 outbreak in Italy	1 week before the SARS-CoV-2 outbreak in Italy	Period 1[a]	Period 2[a]	3 months before the SARS-CoV-2 outbreak in Italy	1 week before the SARS-CoV-2 outbreak in Italy	Period 1[a]	Period 2[a]
Average glucose, mg/dl (mmol/l)	170.6 ± 36.6 (9.5 ± 2.0)	177.7 ± 45.6 (9.9 ± 2.5)	171.8 ± 35.4 (9.5 ± 2.0)	161.0 ± 40.3*# (8.9 ± 2.2)	156.4 ± 18.9 (8.7 ± 1.1)	157.1 ± 20.8 (8.7 ± 1.2)	158.1 ± 17.5 (8.8 ± 1.0)	151.2 ± 15.3 (8.4 ± 0.8)
Standard deviation, mg/dl (mmol/l)	61.3 ± 16.9 (3.4 ± 0.9)	58.9 ± 19.6 (3.3 ± 1.1)	59.5 ± 20.9 (3.3 ± 1.2)	53.2 ± 19.9# (3.0 ± 1.1)	56.9 ± 11.9 (3.2 ± 0.7)	51.8 ± 11.8 (2.9 ± 0.7)	54.0 ± 11.3 (3.0 ± 0.6)	53.6 ± 12.3 (3.0 ± 0.7)
Coefficient of variation, %	35.9 ± 6.8	33.1 ± 6.4	34.3 ± 6.5	33.0 ± 7.9	36.1 ± 4.2	32.8 ± 4.7	34.0 ± 5.6	35.2 ± 6.6
Time in hypo, %	4.2 ± 0.8	3.3 ± 0.9	3.1 ± 0.6	3.2 ± 0.9	4.1 ± 2.2	3.4 ± 3.4	3.1 ± 3.7	3.9 ± 4.2
Time in range, %	56.3 ± 3.8	54.4 ± 4.2	58.1 ± 3.7	65.2 ± 4.2*#	65.1 ± 13.1	65.4 ± 14.3	65.6 ± 13.8	68.3 ± 14.1
Time in hyper, %	39.5 ± 4.2	42.3 ± 4.8	38.7 ± 3.9	31.6 ± 4.4#	30.8 ± 13.3	31.2 ± 15.1	31.3 ± 13.0	27.7 ± 12.7

Values in table are presented as the mean ± SD

SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2 strain

$*p < 0.05$ vs. 1 week before; $^{\#}p < 0.05$ vs. 3 months before

[a] Period 1: from the closure of sport and educational activities to lockdown of the Padova area, when commercial activities and non-essential services were closed; Period 2: the first week after lockdown

Patients who continued working during the lockdown ($n = 13$) had an average age of 45 years, 53.8% were male and average diabetes duration was 24.6 years (and thus longer than that of the group not working). Eight patients were on insulin pump therapy. None of the patients who continued to work showed improvement in any of the measures of glucose control during the lockdown period (period 2) compared to the 3 months or the week before the SARS-CoV-2 outbreak: average glucose, standard deviation, CV%, time in hypoglycaemia, time in range and time in hyperglycaemia remained unchanged (Table 2), as did the number of scans per day. No difference was observed regarding any change in glucose control metrics among those who were on the insulin pump and those who were on a regimen of multiple daily insulin injections.

DISCUSSION

Our data show that, during the first week of lockdown due to the SARS-CoV-2 outbreak in North-East Italy, patients with T1D who stayed at home achieved a significant improvement in glucose control. Among patients with T1D followed at the same clinic who continued working in the same period, many of whom were on insulin pump therapy, no deterioration of glucose control was observed.

The SARS-CoV-2 pandemic represents a huge challenge to public health worldwide [22], and healthcare services have faced severe challenges during outbreaks of the coronavirus disease (COVID-19), resulting in major cut backs in the care provided to people with chronic diseases, including diabetes [23, 24]. Many outpatient clinics have had to change their routine interactions with patient and use telemedicine to monitor patients at home [25]. In Italy, the widespread use of FGM among people with T1D allowed these patients to be remotely connected to the clinic through the cloud. Diabetes professionals were concerned that glucose control could worsen during lockdown because of the limited possibility to exercise and the severe psychologic stress imposed by social distancing in a cultural environment heavily reliant on direct inter-personal relationships. During the outbreak, most non-essential activities were shut down, and most citizens stopped their usual working routine or turned to working at home. However, some people, such as those involved in healthcare or the food supply chain, continued to work during the lockdown. Our observation that glucose control improved during the first week of lockdown in people with T1D who stayed at home is reassuring and suggests that a slowing down of routine activities can have favourable effects on glucose control in the short term. Remarkably, the reduction in average glucose and the increase in time in range were not paralleled by an increased time in hypoglycaemia, which remained stable. We speculate that such an improvement occurred because patients had more time to concentrate on diabetes control and had a more regular lifestyle, including the timing and composition of meals, while not being exposed to workplace stress [26]. In addition, the knowledge that diabetes worsens the outcomes of COVID-19 [27, 28] may have improved patients' awareness and compliance to diabetes management.

To evaluate whether glucose control changed in all patients with T1D during lockdown, irrespectively of whether they stayed at home or not, we included a group of patients who continued working. The observation that glucose control did not improve in this subgroup of T1D patients supports our interpretation. However, the groups of patients who stopped working and those who continued their usual working activities were not comparable because the latter had a better baseline glucose control than those who stayed at home, and > 60% were on insulin pump therapy. Users of pump therapy represent approximately 30% of patients with T1D at our clinic, and 13% of T1D patients nationwide [29]. The frequent use of insulin pump therapy among this group of patients is probably related to the fact that most were healthcare workers and/or shift workers who often need pump therapy to cope with their lifestyle and working schedules. Patients who continued working had a higher time in range at baseline, such that further improvements were more difficult to obtain. Yet, it is

reasonable to assume that these individuals were subjected to stronger challenges during lockdown, including exercise limitations, social distancing, workplace stress, and fear of infection. Therefore, that these patients maintained good glycaemic control is reassuring in terms of their effective self-management of diabetes. We speculate that the use of FGM combined with insulin pump therapy contributed to this effect [30]; for example by limiting diabetes-related distress [31].

We acknowledge that detailed information to interpret the drivers of glucose control during lockdown, such as changes in insulin doses, consumption of snacks and exercise, were not available and should be investigated in future studies. In addition, we included patients with T1D having relatively good glycaemic control and showing frequent sensor use. Therefore, it remains unclear whether the same results would apply to patients with worse glucose glycaemic control or less frequent sensor scans. Finally, we did not analyse glycaemic control in the subsequent weeks of lockdown because most patients were remotely contacted by the physicians from the clinic with advice on how to manage diabetes, thereby introducing bias. Hence, the medium- and long-term impact of lockdown on glucose control remains unknown.

CONCLUSIONS

In summary, we report that glucose control improved in people with T1D who stayed at home during the first week of lockdown due to COVID-19. This observation suggests that slowing down routine activities can have beneficial effects on T1D control in the short term. However, the long-term effects of lockdown and the factors that affect glucose control in this particular situation deserve future investigation.

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