Evaluation of the consequences of the COVID-19 lockdown on glycemic control in type 1 diabetes☆

Consecuencias del confinamiento por la COVID-19 en el perfil glucémico en diabetes mellitus tipo 1

In 2020, our society was struck by the COVID-19 pandemic. Many measures were adopted to prevent the virus from spreading, including lockdowns with permission to leave home only to engage in activities deemed essential. This resulted in a great deal of occupational activity coming to a stop. In Spain, the strictest lockdown period, which lasted from 15 March to 4 May, was followed by a gradual decrease in restrictive measures. Given this situation, society had to adapt to a new reality and with it make lifestyle modifications.

In people with diabetes mellitus type 1 (DM1), a suitable lifestyle is known to play a role in glycaemic control and therefore disease management. In fact, predictive estimates warned of a probable worsening of glycaemic control during this lockdown period.[1]

The objective of this study was to assess the effects of the lockdown on glycaemic control in people with DM1. To achieve this objective, 100 patients using a FreeStyle® system included on the LibreView® platform of the Department of Endocrinology and Nutrition at Hospital Universitario Central de Asturias [Asturias Central University Hospital] with up-to-date data at the time of sample selection were randomly selected. Data were collected for three 14-day periods: pre-lockdown (Pre: 1 February to 15 March), lockdown (LD: 15 March to 4 May) and post-lockdown (Post: 4 May to 31 May). Thirty-two patients were excluded as in at least one period it was not possible to collect data with sensor use over 70%. The following were recorded for each patient: age, sex and parameters for assessment of glycaemic control recommended by Advanced Technologies & Treatments for Diabetes (ATTD) (time in range [TIR] 70–180 mg/dl, time in hypoglycaemia <70 mg/dl and time in hyperglycaemia >180 mg/dl).[2] The SPSS® v.25.0 software programme was used for statistical analysis. Comparisons between the three periods were made using analysis of variance (ANOVA) or Friedman and Wilcoxon tests, depending on whether or not the criteria for a normal distribution were met. Statistical analysis was used to assess differences between the three groups, with $p < 0.05$ corresponding to statistical significance. Where differences were found, subanalyses were performed to look for between-group differences (with $p < 0.017$ corresponding to statistical significance). In the subgroup analysis (by sex, age and glucose management indicator [GMI]), only pre-lockdown and lockdown were compared using percentage change and Student's t test.

The results obtained, shown in Table 1, reflected significant differences in several parameters of glycaemic control during lockdown compared to pre-lockdown. These differences held, without significant changes, in the comparison to the post-lockdown period. Increased TIR (Pre: 55.17%; LD: 61.13%; Post: 62.34%; $p < 0.001$), decreased GMI (Pre: 7.3%; LD: 7.00%; Post: 7.05%; $p = 0.001$) and decreased time in hyperglycaemia (Pre: 39.42%; LD: 34.34%; Post: 32.63%; $p < 0.001$) were found; no significant changes in hypoglycaemia were detected (Pre: 3%; LD: 4%; Post: 4%; $p = 0.522$). In 28 patients (41%), the decrease in GMI was >0.4%.

The subgroup analysis found no significant differences by sex. By age, a difference was indeed found in modification of time in hyperglycaemia (−10.32% in those <45 years of age versus −2.23% in those >45 years of age; $p = 0.032$); however, no differences were detected in GMI or TIR. Patients with an initial GMI > 7.5% showed a greater reduction in time in hyperglycaemia (−23% versus +4%; $p = 0.005$), with no significant differences in TIR or in GMI.

Hence, these results contrasted with the above-mentioned estimates and studies showing worsening of control.[1,3] They were, however, consistent with a larger number of studies showing an improvement in glycaemic control both in adults[4–6] and children and adolescents,[7,8] with a response to lockdown similar to that seen in our sample.

We can conjecture as to the cause of these changes in glycaemic control. Cessation of occupational activity in many patients brought about an increase in free time that might have enabled them to invest in self-care and disease management. Indeed, other studies have shown that patients who did keep their jobs did not experience changes in glycaemic control.[4] Increased diabetes care may have also led to increased use of correct doses of insulin, and with it improved glycaemic control. Nutrition is essential in managing DM1, and changes in eating patterns seen in this period with a higher likelihood of having a regular schedule could have been another factor accounting for this improvement.[9] Physical activity during lockdown was difficult to assess and varied by patient profile,[10] but it predominantly decreased.[3,5,9] Ultimately, we understand that improvements in glycaemic control were primarily due to patients finding themselves with more free time and fewer day-to-day tasks. This shift would have enabled them to focus on improving their self-care, and with that, better managing their disease, thus achieving good outcomes despite their reduced healthcare system access. This demonstrates proper knowledge and capacity for action in relation to diabetes mellitus. It could be useful to determine whether this improvement persisted over time beyond the post-lockdown period or instead patients returned to their prior glycaemic control values when their regular activities resumed.

Our study had a suitable sample size and highly reliable data. Its limitations included its lack of assessment of

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Table 1 Baseline characteristics and glycaemic control parameters.

No. of patients	68					
Female/male	36/32					
Age	46.87 (12.46)					
	Before	During	After	p value	Pre versus LD p value	LD versus Post p value
GMI (%)	7.3 (1.1)	7.0 (0.77)	7.05 (0.7)	<0.001	0.001	0.351
Coefficient of variation (%)	36.17 (10.8)	36.69 (11.5)	36.89 (10.07)	0.61		
Mean blood glucose (mg/dl)	166.58 (4.03)	160.82 (3.30)	158.0 (2.87)	0.065		
Time in range (%)	55.17 (2.28)	61.13 (1.96)	62.34 (1.82)	<0.001	0.003	0.88
Time above target (%)	39.42 (2.23)	34.34 (2.08)	32.63 (1.89)	<0.001	0.006	0.59
Time below target (%)	3.0 (6)	4.0 (6)	4.0 (7)	0.522		
Data capture (%)	93.37 (11)	94.72 (9)	92.68 (8)	<0.001	0.4	<0.001
Readings per day (no.)	8.0 (5)	9.0 (9)	9.0 (9)	0.572		

Results for the three periods expressed in terms of mean and standard deviation. Result for the statistical analysis comparing the three periods (significant if $p < 0.05$). If significant, to its right is a comparison between the pre-lockdown and lockdown periods and between the lockdown and post-lockdown periods (significant if $p < 0.017$).

other parameters of interest in DM1 management, such as weight and insulin units. In addition, sample selection itself excluded patients with suboptimal monitoring use (<70% data capture). It could be of interest to assess whether changes in sensor use occurred in relation to lockdown in this other patient profile.

In conclusion, this study showed that lockdown improved glycaemic control parameters in our sample of patients with DM1 using the FreeStyle® system with a data capture rate over 70%.

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Clinical features of pheochromocytoma masked by VIP co-secretion

Características clínicas del feocromocitoma enmascaradas por la co-secreción de VIP

Vasoactive intestinal peptide-secreting tumors (VIPoma) are rare neuroendocrine tumors (incidence of 0.05–0.2/100,000/yr[1]) first described by Werner and Morrison presenting as a syndrome of watery diarrhea, hypokalemia and achlorhydria.[2] While about 95% of VIPomas arise from the pancreas, some have extra-pancreatic sources.[3,4] VIP-producing pheochromocytomas are extremely rare, with no more than a few cases reported to this date.[5] Due to its several manifestations, management of both conditions can prove to be challenging. We report the case of a woman with a rare VIP-secreting pheochromocytoma presenting as chronic diarrhea and severe hypokalemic metabolic acidosis.

A 63-year-old female was admitted to the Emergency Department for worsening profuse watery diarrhea despite fasting associated with weight loss (14% of total body weight in three months). Upon examination, she was found to be dehydrated and analytical revealed acute kidney injury and hypokalemic metabolic acidosis [*K* 2.8 mEq/L, (reference range (RR) 3.4–5.1); pH 6.9 (RR 7.35–7.45)] requiring intensive intravenous potassium replacement. No increase in inflammatory parameters was found. Mild hypercalcemia (10.9 mg/dL at admission, RR 8.9–10.0) remained after correction of dehydration (10.1 mg/dL), associated with a decreased parathyroid hormone (4.3 pg/mL, RR 15.0–68.3) and normal levels of parathyroid-related protein (<0.5 pmol/L, RR < 1.3). Stool culture and parasitology were negative and endoscopic studies revealed no abnormalities. Abdominal computed tomography (CT) revealed a 6 cm heterogeneous left adrenal mass, and subsequent magnetic resonance imaging (MRI) showed a 5.2 cm partially cystic mass with a hyperintense solid component on T2 (Fig. 1).

She had a history of episodic headaches accompanied by hypertensive crisis (systolic blood pressure > 220 mmHg) three years ago, which resolved after the onset of diarrhea. In the meantime, diabetes mellitus (DM) was diagnosed and initially controlled with metformin 2000 mg and pioglitazone 15 mg daily. Metabolic control has substantially worsened since the onset of diarrhea: HbA1c 9.2% (RR < 6.5) with 40 I.U. of insulin glargine, alogliptin 25 mg and pioglitazone 15 mg daily.

Analysis of the urinary specimen revealed markedly elevated metanephrine (1870 μg/24 h, RR 45–290) and nor-metanephrine (2388 μg/24 h, RR 82–500). VIP plasma levels were elevated, 113 pmol/L (RR < 30), as well as chromogranin A (>700 ng/mL, RR < 100). 123I-metaiodobenzylguanidine (MIBG) scan was performed because it was readily available, revealing high uptake at the topographical location of the left adrenal gland (Fig. 1).

Diarrhea responded poorly to loperamide. The response to treatment with octreotide was impressive, as the patient stopped intravenous fluids, and dehydration and hypokalemia were treated with a dosage of 100 mcg every 8 h. Treatment with octreotide also led to substantial improvements in glycemic control, with a reduction of more than 30% in the total daily insulin dose. Alpha blockade was initiated with phenoxybenzamine, titrated up to 30 mg twice a day, when optimal hemodynamic control was achieved.

Two weeks later, the patient underwent laparoscopic left adrenalectomy without complications. Histological examination revealed a 5.2 cm pheochromocytoma, Ki67 1%, PASS 0. Immunohistochemistry of neoplastic cells showed positivity to chromogranin, synaptophysin, bcl-2 and somatostatin. After surgery, the patient became asymptomatic and plasma VIP and urinary fractionated metanephrine levels normalized (VIP 16.9 pmol/L; metanephrine 59 μg/24 h; and normetanephrine 169 μg/24 h). Two years after surgery, the patient remains disease-free, with no need for antihypertensive therapy and in-target glycemic control with metformin 1700 mg/day (HbA1c 6.8%). The analyzes revealed normal calcium, PTH and vitamin D levels (9.1–9.4 mg/dL, 33.1 pg/mL, and 25 ng/mL, respectively).

We report the case of a middle-aged woman with a history of hypertensive crisis, probably caused by catecholamine excess, which resolved when symptoms related to VIP appeared. Its resolution coinciding with the onset of diarrhea might be explained by the increased secretion of VIP, which has vasodilating properties. VIP not only inhibits the absorption of water and electrolytes by the jejunum and the colon but also increases net intestinal secretion, causing secretory diarrhea.[6]

Coincidental diagnosis of DM with hypertensive crisis is justified, in part, by the pheochromocytoma induced hyperglycemia, and its worsening with the onset of VIP-related symptoms raises the question that the increased glycogenolytic activity of the VIP may play an important role, probably due to its structural homology with glucagon.[6] Also, achievement of better glycemic control with somatostatin analog (SSA) treatment supports our hypothesis, since SSAs are associated with hyperglycemia in other contexts.

Although the responsiveness of VIP-secreting pheochromocytomas to SSA has been questioned by Quarles et al.[7] due to a reported scarcity of somatostatin receptors, our patient had an excellent response with a relatively small dose of octreotide, with a drastic reduction in the number of dejections, reaching normokalemia with no acid-base disorders. In addition, control of diabetes was significantly improved. In