Letter to the Editor

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Severity in pediatric type 1 diabetes mellitus debut during the COVID-19 pandemic

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During the period of March 21st to May 6th 2020, the region of Madrid, epicenter of Spain's coronavirus disease 2019 (COVID-19), was under home confinement and health care resources were redistributed. Pediatric care was centralized in two tertiary hospitals in the region, one of them being *Hospital Infantil Universitario Niño Jesús*. Although children appear to be less frequently [1] and severely affected by COVID-19 than adults [2], they can develop other intercurrent illnesses. Previous reports have documented 46–51 [3] and 73–88% [4] decreases in pediatric emergency room attendance during the COVID-19 outbreak, with the latter study including two cases of severe diabetic ketoacidosis requiring Pediatric Intensive Care Unit (PICU) admission [3]. A nationwide German pediatric study reported a significant increase in the

incidence and severity of diabetic ketoacidosis during the COVID-19 pandemic [5].

A single-center retrospective observational study was undertaken with the aim to compare the presentation characteristics of pediatric patients (0–18 years) with new-onset type 1 diabetes mellitus (T1DM) between March 21st and May 6th 2020, to those diagnosed prior to the pandemic period. Local Ethical Committee approval was obtained. Epidemiological, clinical, and biochemical data as well as the therapeutic approach and clinical course were collected and extracted from the patients' medical records.

During the outbreak, 10 patients, the pandemic group, presented with T1DM debut in our Emergency Department (ED); whereas in the same time span in the years 2019 and 2018, its incidence was 2 and 1, respectively. The median age (P_{25} – P_{75}) of the patients during the outbreak was 8.5 years (5.25–10), whereas in our center during the previous years, it was 13.08 (9.41–14.16) in 2019 and 10.7 (8.5–12.2) years in 2018. The findings in the pandemic group were compared to two different control groups: A) 10 patients diagnosed in previous years, 2018 ($n=5$) and 2019 ($n=5$) and B) 10 age-adjusted controls, as it is known that in younger children the possibility of diabetic ketoacidosis is greater than in older children as the former have a tendency for a more delayed hospital presentation ($n=4$ from the year 2018, $n=5$ from 2019 and $n=1$ from January 2020).

The characteristics at presentation upon ED arrival are shown in Table 1. All patients presented with polyuria, 92% with polydipsia, and 65% indicated recent weight loss. Initial venous blood gas results, need for PICU admission, and length of time to transition to subcutaneous insulin, and oral diet were significantly different between both groups. Seven patients in the pandemic group were admitted to PICU because of severe hypokalemia (3/10), persistent acidosis (3/10), neurologic signs (1/10), and/or young age (2/10). No patient developed cerebral edema or any other fatal complication. Two patients in the pandemic group tested positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) by reverse transcriptase – polymerase chain reaction (RT-PCR) and

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Table 1: Demographic, clinical, and biochemical characteristics upon emergency department arrival and subsequent hospital progress of children during the COVID-19 period vs. controls.

	Pandemic group (n=10)	Age-matched controls (n=10)	p-Value* between pandemic group and age-matched controls	Time frame-matched controls from 2018 and 2019 (n=10)	p-Value* between pandemic group and time frame-matched 2018 and 2019 controls
Upon ED arrival					
Males/females	6/10	4/10	NS	2/10	NS
Age at presentation (median, P ₂₅ –P ₇₅) years	8.5 (5.25–10)	8.5 (6.25–9.25)	NS	12 (9.75–14)	0.01
Health care provider contact prior to ED attendance	7/10	6/10	NS	5/10	NS
Expansion with saline bolus of 20 ml/kg (instead of 10 ml/kg)	6/10	0/10	0.01	1/10	0.05
Kussmaul breathing pattern	6/10	4/10	NS	0/10	0.01
Initial pH (median, P ₂₅ –P ₇₅)	7.08 (7.02–7.31)	7.33 (7.2–7.37)	0.05	7.36 (7.31–7.40)	0.006
Initial HCO ₃ ⁻ (median, P ₂₅ –P ₇₅) mmol/l	6.1 (5.2–17.4)	18.5 (11.3–22)	0.04	22 (16.3–25.7)	0.004
Initial base excess (median, P ₂₅ –P ₇₅) mmol/l	-21.9 (-23.6–6.8)	-3.7 (-15–0.2)	0.03	-2.9 (-10–0.5)	0.007
Initial pCO ₂ (median, P ₂₅ –P ₇₅) mmHg	23.5 (18.7–33.4)	31.5 (26.7–38.2)	0.04	36.5 (26.8–43.5)	0.01
PICU admission	7/10	1/10	0.02	0/10	0.003
Time to achieve pH _{7.30} , HCO ₃ ⁻ ≥15 mmol/l and BOHB<0, 6 mmol/l (median, P ₂₅ –P ₇₅) h	17 (1.5–23)	4 (0–14.8)	NS	0 (0–2)	0.006
Time to transition to subcutaneous insulin and oral diet (median, P ₂₅ –P ₇₅) h	50 (37.5–57)	29.5 (18–48)	0.01	26.5 (15.8–36)	0.03

ED, Emergency department; PICU, pediatric intensive care unit; BOHB, beta-hydroxybutyric acid; NS, No statistical significance. *Numerical variables were compared by U Mann–Whitney test and ratios were compared using Chi-square. Statistical significance was considered provided p<0.05. Statistically significant results are highlighted in bold.

presented associated mild respiratory signs, thus none required specific SARS-CoV-2 therapy. A caveat to this study is the lack of availability at the time to perform SARS-CoV-2 antibody testing.

Our findings confirm a significant increase in the severity of presentation of new-onset T1DM cases during the COVID-19 pandemic, in line with a previous German study [5], regardless of the control group used for comparison. Given the severity of the gasometry results along with the high rate of PICU admission in the pandemic group, a reticence to seek hospital assistance is assumed. This delayed access to health care reflects parental/caregiver's apprehension and desire to minimize risk exposure to a conceivably contagious medical environment. Additionally, in some cases, families may have trivialized signs to avoid saturating EDs during the lockdown period. Detrimental morbimortality consequences can develop from late hospital access during diabetic ketoacidosis, including decease. Of note, during the COVID-19 pandemic period, the age at presentation of T1DM debut was younger than in the previous years in our center. A recent publication has speculated on the influence of COVID-19 *per se* on the etiology of T1DM onset [6]; however, it is possible that the higher vigilance of parents being confined resulted in the younger age of presentation of our "pandemic group" children. Another plausible explanation for this finding could involve the fact that our hospital became a referral center for half of the pediatric population of Madrid between the period of March 21st and May 6th 2020 and thus represented a partially different population.

While the management of known T1DM patients during the COVID-19 pandemic has been addressed [7, 8], often advocating for promotion of telemedicine, the question of how to best avoid delayed new-onset diagnosis remains unanswered. Albeit seven patients had contacted a medical provider, hours prior to attending the ED during the pandemic, the overwhelming situation faced by ambulatory pediatricians and medical emergency telephone services may have contributed to not identifying signs effectively and promptly enough compared to the normal occurrence in former years. Revision of various national and international institutional parental guidelines regarding alarming signs that should encourage ED consultation evidenced the fact that cardinal signs of T1DM were often not included. Unequivocal and easily accessible

instructions for caregivers regarding red flag signs to identify in children are paramount during outbreaks so as to avoid deferred/missed diagnosis of severe and potentially life-threatening conditions.

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Ethical statement: The patients' parents gave informed consent for the publication of the clinical information. The manuscript does not contain data that could potentially lead to the identification of the patients.

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