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Artigo Original

# Impact of COVID-19 in New-Onset Type 1 Diabetes Mellitus in a Large Portuguese Pediatric Diabetes Center

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A B S T R A C T

***Introduction:*** Our aim was to characterize new-onset type 1 diabetes mellitus (T1D) cases in a pediatric population referred to a large pediatric diabetic center throughout the first year of the COVID-19 pandemic, comparing it to previous years.
***Methods:*** Retrospective study including patients under 18 years with new-onset T1D, from March 12th 2020 to March 11th 2021. A control group was defined using data on patients under 18 years with new-onset T1D referred to the same hospital in the 3 previous years (from March 2017 to March 2020). Data was analyzed using SPSS. A *p* value of 0.05 was used as threshold of significance.
***Results:*** Between March 12th 2020 and March 12th 2021, 44 patients were diagnosed with new-onset T1D. The control group included 96 patients, resulting in an incidence of 32 cases/year (37.5% rise). January 2021 was the month with the higher number of diagnosis, corresponding to the peak of novel SARS-CoV-2 infections. During the pandemic, new-onset T1D cases in children under 2 years-old doubled, when comparing to mean incidence in previous years. Median delay to diagnosis was not significantly different from previous years. Diabetic ketoacidosis (DKA) at presentation was present in 50% of cases that were diagnosed after lockdown, increasing substantially from previous years (38.5%). DKA's severity was also significantly higher (40.9%, $p$=0.04), as were Intensive Care Unit admission (13.6%, $p$=0.04).
***Conclusion:*** Despite the existance of molecular pathways that could lead to islet cell injury, the role of the new coronavirus in the pathogenesis of DKA and T1D onset is still unclear. Disease severity could also be related to a higher proportion of younger children.

## Impacto da COVID-19 na Diabetes Mellitus Inaugural num Centro de Diabetologia Pediátrica Portuguesa

R E S U M O

***Introdução:*** O nosso objetivo foi caracterizar os casos de diabetes *mellitus* tipo 1 (T1D) inaugurais na população pediátrica referenciada a um centro de diabetes pediátrica durante o primeiro ano da pandemia por COVID-19, comparando-os com os anos anteriores.
***Métodos:*** Estudo retrospectivo incluindo doentes com menos de 18 anos com T1D inaugural, de 12 de Março de 2020 a 11 de Março de 2021. Foi definido um grupo de controlo a partir de dados de doentes com menos de 18 anos com T1D inaugural referenciados ao mesmo hospital nos 3 anos anteriores (de Março de 2017 a Março de 2020). Os dados foram analisados utilizando SPSS. Foi utilizado um valor *p* de 0,05 como limiar de significância.

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***Resultados:*** Entre 12 de Março de 2020 e 12 de Março de 2021, foram diagnosticados 44 doentes com T1D. O grupo de controlo incluiu 96 pacientes, com incidência de 32 casos/ano (aumento de 37,5%). Janeiro de 2021 foi o mês com o maior número de diagnósticos, correspondendo ao pico das novas infecções por SARS-CoV-2. Durante a pandemia, os casos de T1D em crianças com menos de 2 anos duplicaram quando comparados com a incidência média nos anos anteriores. O atraso médio no diagnóstico não foi significativamente diferente dos anos anteriores. A cetoacidose (CAD) como forma de apresentação ocorreu em 50% dos casos diagnosticados após o decretar de confinamento, aumentando substancialmente em relação aos anos anteriores (38,5%). A gravidade da CAD foi também significativamente maior (40,9%, $p$=0,04), tal como a admissão na Unidade de Cuidados Intensivos (13,6%, $p$=0,04).

***Conclusão:*** Apesar da existência de mecanismos moleculares comuns que poderiam conduzir a lesão do tecido pancreático, o papel entre o papel do novo coronavírus na patogénese da T1D inaugural é ainda incerto. A maior gravidade da CAD poderá também estar relacionado com uma maior proporção de casos em crianças mais novas.

## Introduction

December 2019 marked the unsuspicious beginning of a global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Since then, SARS-CoV-2 associated disease (COVID-19) has caused a profound shift in countless aspects of society. One of these aspects was healthcare access, both emergent and routine,[2] giving way to concerns that delayed referral to healthcare could promote increased severity of non-COVID-19 related diseases.[3,4] Simultaneously, SARS-CoV-2 has been increasingly recognized as a potent inflammatory trigger, prompting immune deregulation through mechanisms such as molecular mimicry and "cytokine storms," the most striking pediatric example being the multisystem inflammatory syndrome in children (MIS-C).[5,6]

Previous publications have highlighted a seeming rise in type 1 diabetes mellitus (T1D) diagnosis, as well as increased severity for new-onset T1D.[7] Higher risk for diabetic ketoacidosis (DKA) in patients with known T1D has also been reported.[8] Both delayed access to healthcare and SARS-CoV-2 immunogenicity have been enlisted as possible explanations for these findings.[9,10]

We aimed to further contribute to this discussion, by characterizing new-onset T1D cases in a pediatric population referred to a large pediatric diabetic center throughout the first year of the COVID-19 pandemic, comparing it to previous years, namely in demographic characteristics, clinical and biochemical presentation, as well as DKA's incidence and severity.

## Methods

A retrospective study performed in a Pediatric Endocrinology Unit of a level III hospital was performed, including children and adolescents under 18 years with new-onset T1D, from March 12$^{th}$ 2020 (time of the first lockdown imposition in Portugal) to March 11$^{th}$ 2021 (12 months duration). For the control group, clinical, epidemiological and laboratorial data on children and adolescents under 18 years with new-onset T1D referred to the same hospital in the 3 previous years (from March 2017 to March 2020) was collected.

T1D was established based on the usual diagnostic criteria.[11] Patients with incomplete information regarding presentation status were excluded from the study.

Data was collected from electronical clinical files and included: age at presentation; gender; co-morbidities; family history of T1D, type 2 diabetes mellitus (T2D), or other autoimmune disease; symptoms and their duration; blood glucose, ketonemia, pH, bicarbonate and HbA1C at presentation; SARS-CoV-2 protein chain reaction (PCR) status; type of hospitalization (ward/Paediatric Intensive Care Unit, PICU).

Clinical presentation of T1D was categorized as: hyperglycemia, hyperglycemia with ketonemia (≥0.6 mmol/L), and DKA. DKA was classified as: mild (pH <7.3 and/or bicarbonate <15 mmol/L), moderate (pH <7.2 and/or bicarbonate <10 mmol/L), and severe (pH <7.1 and/or bicarbonate <5 mmol/L).

Data was analyzed using SPSS, 21$^{th}$ version software (SPSS, Chicago, IL) for Mac. Continuous data were compared by use of paired and unpaired Student t test whenever applicable. Independent proportions were compared by use of the 2-tailed Fisher exact test. A $p$ value of 0.05 was used as the threshold of significance. Results are presented as median (min., max.) unless stated otherwise.

## Results

### Incidence

Our study included 140 patients with new-onset T1D, 44 of which diagnosed between March 12$^{th}$ 2020 and March 12$^{th}$ 2021. The control group was composed of 96 patients who were diagnosed between March 12$^{th}$ 2017 and March 11$^{th}$ 2020, resulting in an incidence of 32 cases/year. This reflected a 37.5% rise in new-onset T1D cases.

While in previous years, a mean incidence of 2.7 cases/month was observed, during the pandemic period, the monthly incidence of new T1D cases exceeded this figure in most months, with a mean of 3.6 new cases/month. In the group of patients diagnosed during the COVID-19 pandemic, the number of T1D diagnosis steadily increased until September, with January 2021 being the month with the higher number of diagnosis (8 cases), doubling the mean monthly incidence that year. January 2021 also corresponds to the peak of novel SARS-CoV-2 infections in the country. The annual distribution of T1D cases can be appreciated in Fig. 1, whereas the incidence of new SARS-CoV-2 cases can be found in Fig. 2.

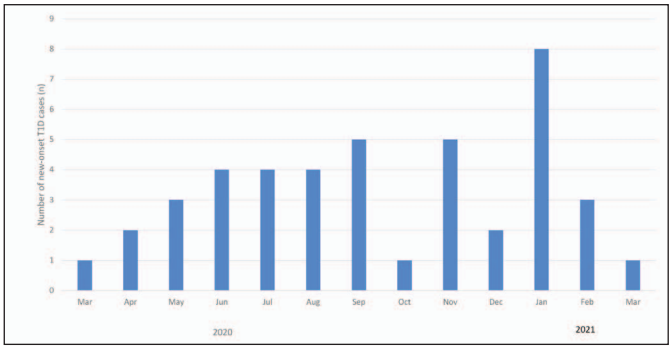


*Figure 1.* Annual distribution of new-onset T1D cases between 2020 and 2021.

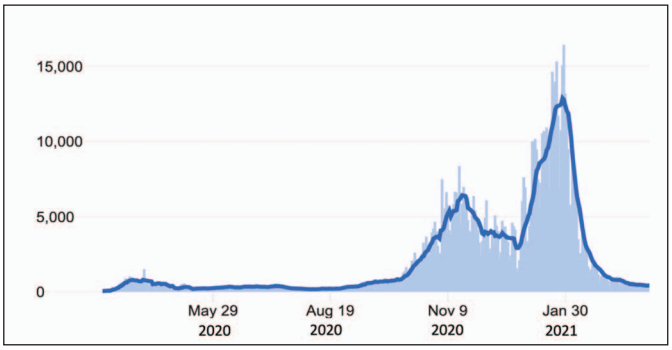


*Figure 2.* Incidence of SARS CoV-2 infections in Portugal (Data from Center for Systems Science and Engineering at Johns Hopkins University)

## Demographic characteristics

Patients diagnosed during the pandemic had a median age of 9 years (+/- 4.2, min. 0.5, max. 15.8 years), whilst patients in the control group had a median age of 10.7 years (+/- 4.5, min. 0.9, max. 17.9 years). This difference did not reach statistical significancy. Overall, the incidence of new-onset T1D increased both in the group of patients aged less than 10 years (22 cases *vs* 15.7/year in the control group) and of those aged 10 years or more (22 cases *vs* 16.7/year in the control group). Peak incidence was observed in the group of patients aged 10 to 14 years in both groups (43.2% *vs* 41.7% in the control group). From March 2020 on, new-onset T1D cases in children under 2 years-old doubled (2 cases), when comparing to mean incidence in previous years (1 case/year).

Gender distribution was similar in the two groups, with a slight male predominance of cases (52.3% *vs* 53.1% in the control group) (Table 1).

*Table 1.* Demographic characteristic of both groups

| | COVID group | Control group | Significance |
|---|---|---|---|
| **No.** | 44 | 96 | - |
| **Gender, no. (%)** | | | |
| Female | 21 (47.7) | 45 (46.9) | NS |
| Male | 23 (53.2) | 51 (53.1) | NS |
| **Age group, no. (%)** | | | |
| < 2 | 2 (4.5) | 3 (3.1) | NS |
| ≥ 2-5 | 5 (11.4) | 19 (16.7) | NS |
| ≥ 5-10 | 15 (34.1) | 25 (27.1) | NS |
| ≥ 10-15 | 19 (43.2) | 40 (42.7) | NS |
| ≥ 15 | 3 (6.8) | 10 (10.4) | NS |

NS: non significant.

Family history of autoimmune diseases was present in 50% of the cases in the control group, while being slightly less prevalent (43.2%) in the cases diagnosed during the pandemic. T1D familial history was present in 27.3% of cases during the pandemic and in 15.6% in the previous years.

## Clinical characteristics

The duration of symptoms was of 2 to 4 weeks, identical before and after lockdown imposition (29.2% and 31.7% respectively). However, the number of patients presenting with symptoms for less than a week was much higher in the pandemic group compared to the control group (20.5% *vs* 9.4%, not statistically significant).

There were no statistically significant differences between presenting symptoms before and after the pandemic. Polydipsia was the most frequent symptom (88.5% and 84.1% respectively), followed by polyuria (82.3% and 75% respectively) and weight loss (72.9% and 61.4% respectively).

DKA at presentation was present in the majority (50%) of cases that were diagnosed after lockdown, increasing substantially from previous years (38.5%) (Fig. 3). DKA's severity also augmented in a statistically significant manner (40.9% of DKA cases vs 18.9% in previous years, $p$=0.04).

PICU admissions were also significatively higher: 13.6% subjects required admission to the PICU during the pandemic, compared to just 4.2% in prior years ($p$=0.04) (Fig. 4).

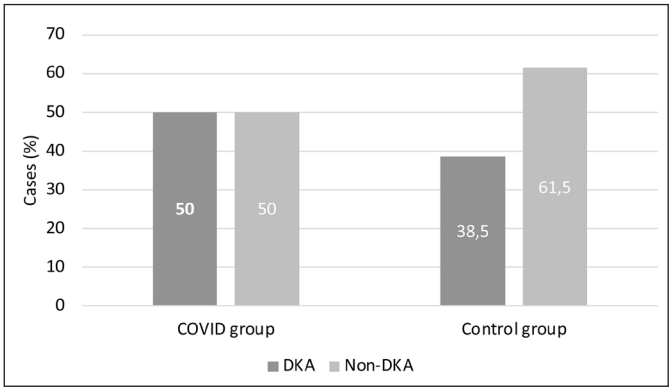


*Figure 3.* Proportion of DKA and non-DKA presentation in patients during the pandemic, comparing to the control group.

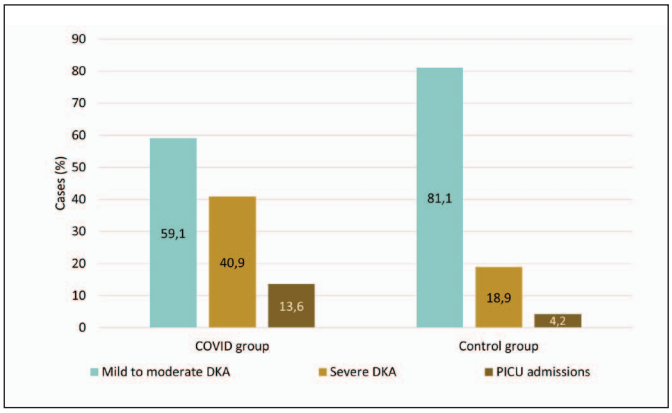


*Figure 4.* Severity and PICU admissions comparison between T1D cases diagnosed during the pandemic, compared to the control group.

## Biochemical characteristics

Mean A1C hemoglobin was of 11.2% (+/- 3.2%) during the pandemic, slightly lower than in previous years (11.4% +/- 2.9%), although this finding was not statistically significative.

## COVID-19 infection

Since the beginning of the pandemic period, all patients were tested for SARS-CoV-2 via a PCR test, as this was routine for patients admitted to our center's infirmaries. Only 2 patients had a positive PCR test for SARS-CoV-2: an 8-year boy who presented with mild DKA, and a 13-year old adolescent, presenting with moderate DKA.

Serologies for SARS-CoV-2 were not performed regularly on

the patients diagnosed initially, as the technology was not available.

## Discussion

A higher number of pediatric new-onset T1D cases was observed during the first year of COVID-19 in our center compared to previous years. The cases' severity was also significantly higher, with a substantial rate of PICU admissions. Various factors could have contributed to this finding. The hypothesis that delayed access to healthcare facilities, as it was seen with other pathologies[3,4] could have taken a part in exponentiating DKA severity was not sustained by our data, as the average delay to diagnosis was not significantly different from previous years. Nevertheless, and albeit not statistically significant, a higher number of patients presented to the emergency room with short-lasting symptoms, a finding that remains unexplained.

A possible role of viral infections in T1D onset has been postulated for over 40 years.[12-14] Rotavirus and enterovirus have frequently been proposed as likely culprits, although not exclusively – in 2009, during the aftermath of the SARS-CoV-1 pandemic, it was suggested that coronavirus used angiotensin converting enzyme 2 (ACE2), as the cellular entry point in pancreatic islet cells.[15-17] A similar pathway was proposed for SARS-CoV-2 after the publication of several case series where a high prevalence of hyperglycemia was observed in adult patients that could not be fully explained by corticoid therapy and the viral infection itself; this fact imposed an extra risk for adverse outcomes.[18-20] In addition to ACE2 receptors, interleukin-6 has also been thought to play a role in cytokine-mediated pancreatic damage, since it is one of the main molecules involved in both Th1 autoimmune islet cell destruction seen in T1D and COVID-19-related cytokine storms.[21-23] The finding that the months when more T1D cases were diagnosed paralleled the period when more SARS-CoV-2 infections were diagnosed in Portugal, creating somewhat overlapping graphs (Figs. 1 and 2, respectively), could further support this hypothesis.

The higher overall severity of DKA could also be partially explained by the higher number of cases in children under 5 years old, which has been identified as a risk factor by recent studies.[24-26] In another recently published study, we have observed a higher incidence of DKA in younger ages.[27] Previous studies have additionally shown increasing trends for new-onset T1D cases in this age group.[28,29] Reasons for this include a lower index of suspicion and possibly a more aggressive inflammatory islet cell destruction, in line with recent findings that a specific type 1 endotype may exist in this age group.[30,31]

The variation trends of new onset T1D cases have been studied for multiple decades, with reported peak incidence cyclicity of 4 to 6 years.[32] No clear rationale has been stablished, although viral epidemics have been previously implicated in season variations of T1D incidence.[33] The possibility that we are heading towards a new high-incidence period, and the contribution of present-day viral pandemics to such pattern variability, namely COVID-19, can only be guessed at the present time.

## Limitations

We find that the small cohort of this study was the main limitation, constraining its power. A multicentric approach would help minoring this aspect. Serological SARS-CoV-2 tests were not performed routinely during the first months of the pandemic, which could have supported the link between infection and T1D onset, even though causality would always be hard to stablish with a retrospective study.

## Conclusion

Upon the emergence of the SARS-CoV-2 pandemic, we found a higher number of T1D cases, as well as more frequent and more severe DKA. Longer delay to diagnosis did not seem to significantly contribute to this finding. Despite the existance of molecular pathways that could lead to islet cell injury, the role of the new coronavirus in the pathogenesis of DKA and T1D onset is still unclear. Disease severity could also be related to a higher proportion of younger children. Broader studies are lacking for more definitive conclusions to be drawn.

## Contributorship Statement / Declaração de Contribuição:

FBC, AL, CR, SB and AMG collected the data.
FBC analyzed the data and wrote the manuscript.
CD, ALF, JG, RP, LL and CL revised and approved the final manuscript.

## Responsabilidades Éticas

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
**Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo.
**Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
**Proteção de Pessoas e Animais:** Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
**Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.

## Ethical Disclosures

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**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of data from patients.
**Protection of Human and Animal Subjects:** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
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