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ORIGINAL ARTICLE

Impact of SARS-CoV-2 pandemic on Inaugural Diabetes cases in pediatric age in the Autonomous Region of Madeira

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Abstract

The objective of this work was to carry out a comparative analysis of inaugural diabetes in pediatric age in the Autonomous Region of Madeira (ARM) before and after the onset of the SARS-CoV-2 pandemic. A meta-analysis published in August 2022 in the Nature Journal found a statistically significant increase in the number of patients who presented with diabetic ketoacidosis among patients newly diagnosed with type 1 diabetes mellitus (T1DM) during the pandemic. The same was not verified in ARM. Some of the factors presented are that in ARM there was never a period of total confinement for the general population, and medicine was always practiced close to the population, among others. Family history was the only study variable in which there was a statistically significant difference between the two groups. This result may show that cases of diabetic ketoacidosis diagnosed during the pandemic, some of them probably in patients who were previously infected with SARS-CoV-2, may have a different pathophysiology in which genetic factors play a lesser role. As T1DM is a frequent disease in children, health professionals must be alert and have a high degree of suspicion given the diversity of initial presentations that this disease can have and regularly assess glucose and HbA1c. More studies should be carried out to try to find out what justifies this population not being vulnerable to an increase in the number of cases of inaugural diabetes or to their greater severity.

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INTRODUCTION

Located in the Atlantic Ocean, the Autonomous Region of Madeira (RAM, Região Autónoma da Madeira) and the Azores archipelago make up Portugal's island territories. Approximately 40,000 children and adolescents inhabit the RAM.

COVID-19 was declared a public health emergency by the World Health Organization (WHO) in January 2020 and elevated to a pandemic status in March 2020. A highly infectious condition, COVID-19 causes a wide array of symptoms. In pediatric patients, however, about 80% of cases present as flu-like syndromes with no complications. However, cardiovascular disorders and kidney failure have been reported in critically ill patients and individuals with risk factors or comorbidities such as high blood pressure, older age, cardiovascular diseases, or diabetes.[1]

Type 1 diabetes mellitus (T1DM) is an autoimmune disease with a genetic basis. Environmental factors, such as chemical exposure, food, viral infection, and autoimmune stimuli, contribute to its pathophysiology. An early diagnosis is crucial to prevent the progression of diabetic ketoacidosis, a severe complication of T1DM.[2]

An association has been described between COVID-19 and the increase in the number of new cases of diabetes and ketoacidosis, although studies have offered contradictory information.[3-12]

OBJECTIVES

This article offers a comparative analysis of the pediatric cases of diabetes in the Autonomous Region of Madeira before and after the start of the COVID-19 pandemic.

METHOD

Considering that the first case of COVID-19 in the RAM was reported on March 17, 2020, and that the WHO elevated the disease to a pandemic status in March 2020, we divided the time horizon of our analysis into two 26-month-long periods, one before and the other after the start of the pandemic, to carry out a comparative statistical analysis of two groups.

PRE-COVID-19 corresponds to the time interval between April 1, 2017, and May 31, 2019. POST-COVID-19 locates between April 1, 2020, and May 31, 2022.

A retrospective and cross-sectional analysis was carried out to include all new cases of diabetes diagnosed in the pediatric emergency service of the Funchal Central Hospital, on Madeira Island, in the periods above, recorded on the software system ATRIUM ®.

The following variables were recorded in Microsoft Office Excel®: age, sex, time interval between onset of symptoms and diagnosis, polydipsia, polyuria, polyphagia, weight loss, asthenia, nausea and vomiting, abdominal pain, glucose, HCO_3^- and serum lactate, pH at admission, family history of diabetes mellitus, hyperglycemia, hyperglycemia with ketosis, ketoacidosis, severity of ketoacidosis, days spent in a pediatric ward and in an intensive care unit (ICU).

The chi-square test and Fisher's exact test were used to prove whether there were statistical differences between the categorical variables. Statistical differences between continuous variables were analyzed using Student's t-test for age and non-parametric tests for all other continuous variables.

As illustrated in Table 1, patients were categorized into three groups: hyperglycemia, hyperglycemia with ketosis, and ketoacidosis. The severity of ketoacidosis was described as mild, moderate, or severe.

RESULTS

The PRE-COVID-19 group consisted of 10 patients, and the POST-COVID-19 group had 11 patients. The average age at diagnosis was 10.6 years in the PRE-COVID-19 group and 11.4 years in the POST-COVID-19 group. The median time until the onset of symptoms was longer in the PRE-COVID-19 group (17.5 days versus 14 days in the POST-COVID-19 group).

Polydipsia was reported in 90% of patients in the PRE-COVID-19 group and 81.8% of patients in the POST-COVID-19 group. Polyuria was reported in 90% of patients in the PRE-COVID-19 group and 72.7% of patients in the POST-COVID-19 group. Polyphagia was found in 40% of patients in the PRE-COVID-19 group and 36.4% in the POST-COVID-19 group.

Weight loss was more frequent in the POST-COVID-19 group than in the PRE-COVID-19 group (81.8% versus 80%, respectively). Asthenia was reported in 40% of patients in the PRE-COVID-19 group and 27.3% in the POST-COVID-19 group.

The number of cases of nausea and vomiting varied substantially between the groups (10% in the PRE-COVID-19 group versus 45.5% in the POST-COVID-19 group).

The maximum glucose levels recorded were 1177 mg/dL in the PRE-COVID-19 group and 988 mg/dL in the POST-COVID-19 group. The median glucose levels in the PRE-COVID-19 and POST-COVID-19 groups were 582 mg/dL and 499 mg/dL, respectively.

The median HCO_3- levels were 12.3 mmol/L and 15.3 mmol/L in the PRE-COVID-19 and POST-COVID-19 groups, respectively.

Table 1. Patient categorization on admission.

Classification	
Hyperglycemia	Glucose > 200mg/dL + pH≥ 7.30
Hyperglycemia with ketosis	Glucose > 200mg/dL + pH≥ 7.30 + [Ketonemia ≥ 3 mmol/L and/or moderate to severe Ketonuria]
Ketoacidosis	pH <7.30 and/or HCO_{3-} ≤ 15 mmol/L
Mild	pH 7.20-7.29 or HCO_{3-} 10-15 mmol/L
Moderate	pH 7.10-7.19 or HCO_{3-} 5-10 mmol/L
Severe	pH < 7.10 or HCO_{3-} < 5 mmol/L

The median pH at the time of admission and the minimum and maximum values for each group were equal: median of 7.2, minimum of 6.9, and maximum of 7.4.

Median lactate levels were 1.1 mmol/L and 1.6 mmol/L in the PRE-COVID-19 and POST-COVID-19 groups. The maximum values were 2.4 mmol/L in the PRE-COVID-19 group and 6.2 mmol/L in the POST-COVID-19 group.

Hemoglobin A1C (HbA1C) was higher in the POST-COVID-19 group compared to the PRE-COVID-19 group, with median levels of 15.3% and 11.3%, respectively. Although the difference was not statistically significant, in addition to a higher median level, the minimum and maximum values were higher in the POST-COVID-19 group.

Family history of DM was the only variable with a statistically significant difference between the groups. Seventy percent of patients had a positive family history of DM in the PRE-COVID-19 group, against 18.2% in the POST-COVID-19 group (p=0.017).

Regarding the conditions associated with the onset of diabetes, hyperglycemia was observed in 18.2% of patients in the POST-COVID-19 group.

Hyperglycemia with ketosis was seen in 30% and 18.2% of patients in the PRE-COVID-19 and POST-COVID-19 groups, respectively.

Ketoacidosis was observed in 70% and 63.6% of patients in the PRE-COVID-19 and POST-COVID-19 groups, respectively. The proportion of cases with moderate ketoacidosis was the same in both groups (42.9%); mild ketoacidosis was seen in 42.9% of patients in the PRE-COVID-19 group and 28.6% in the POST-COVID-19 group. Severe cases of ketoacidosis were seen in 14.3% of patients in the PRE-COVID-19 group and 28.6% in the POST-COVID-19 group.

The length of stay was calculated as the total number of days spent in a pediatrics ward or ICU.

Ninety percent and 90.9% of patients in the PRE-COVID-19 and POST-COVID-19 groups required hospitalization in a pediatrics ward for a median of five and six days, respectively.

Ten percent of patients in the PRE-COVID-19 group and 18.2% of patients in the POST-COVID-19 group were admitted to an ICU. The median length of stay was one day in the PRE-COVID-19 group and 3.5 days in the POST-COVID-19 group.

The median total number of days of hospitalization was 4.5 days in the PRE-COVID-19 group and six days in the POST-COVID-19 group.

Although the POST-COVID-19 group had a higher median number of days spent in a pediatric ward and ICU than the PRE-COVID-19 group, the difference was not statistically significant.

The POST-COVID-19 group had a higher proportion of cases of severe ketoacidosis than the PRE-COVID-19 group, but the difference was not statistically significant.

The results are described in greater detail in Table 2.

DISCUSSION

A meta-analysis published in August 2022 in Nature Magazine, which included 24 studies with a total of 124,597 children newly diagnosed with diabetes, found a statistically significant increase in the number of patients with diabetic ketoacidosis among individuals diagnosed with DM1 during the pandemic, especially severe forms of ketoacidosis when compared to the respective groups before the pandemic.[11]

The same, however, did not occur in the RAM.

One reason that might explain the increase in the number of cases of severe ketoacidosis is the delay in going to an emergency care unit for fear of contracting SARS-CoV-2 infection and the strict confinement measures in effect at the time.[12,13]

Total confinement was never fully enforced in the RAM. Measures in this direction comprised mandatory isolation at home for certain hours of the afternoon, which were in effect for several months.

During the pandemic, a telephone line was created in the region so that local healthcare could continue to be provided. The line remains operational to this day. It aims to address parents' concerns, guide cases that can be treated remotely, or recommend that patients seek emergency care when indicated.

A possibility is that the incidence and severity of diabetes may not have increased in the region because the population continued to seek emergency care in serious situations, and face-to-face care was maintained.

The RAM has only one public hospital, which means that all new cases of diabetes are treated at the same hospital. The Funchal Central Hospital is the only place in the entire region with a 24-hour pediatric emergency room and the only pediatric hospital in operation. The hospital has a pediatric ICU equipped to receive patients with severe ketoacidosis. Although several health centers and private clinics serve children and adolescents, all refer cases that require immediate care and surveillance to the Funchal Central Hospital.

Table 2. Comparative analysis between PRE-COVID-19 and POST-COVID-19 groups.

Variables	April 2017 - May 2019	April 2020 – May 2022	*p-value*
Number of patients	10	11	-
Age at diagnosis (years)	10.6±4.6	11.4±3.3	*0.664*
Male Sex (%)	7 (70.0)	7 (63.6)	*0.757*
Time interval from onset of symptoms to diagnosis (days)	17.5 (2-120)	14.0 (1-180)	*0.654*
Polydipsia (%)	9 (90.0)	9 (81.8)	*0.593*
Polyuria (%)	9 (90.0)	8 (72.7)	*0.314*
Polyphagia (%)	4 (40.0)	4 (36.4)	*0.864*
Weight loss (%)	8 (80.0)	9 (81.8)	*0.916*
Asthenia (%)	4 (40.0)	3 (27.3)	*0.537*
Nausea and vomiting (%)	1 (10.0)	5 (45.5)	*0.072*
Abdominal pain (%)	4 (40.0)	3 (27.3)	*0.537*
Glucose, mg/dL	582 (374-1177)	499 (403-988)	*0.468*
HCO3, mmol/L	12.3 (4.0-23.3)	15.3 (3.0-25.0)	*0.603*
pH on admission	7.2 (6.9-7.4)	7.2 (6.9-7.4)	*0.656*
Lactate, mmol/L	1.1 (0.4-2.4)	1.6 (0.6-6.2)	*0.605*
Hba1c (%)	11.3 (10.5-14.5)	13.7 (12.0-15.6)	*0.171*
Family history of DM (%)	7 (70.0)	2 (18.2)	*0.017*
Hyperglycemia (%)	0 (0.0)	2 (18.2)	*0.156*
Hyperglycemia with ketosis (%)	3 (30.0)	2 (18.2)	*0.525*
Ketoacidosis (%)	7 (70.0)	7 (63.6)	*0.757*
Severity of ketoacidosis (%)			
Mild	3 (42.9)	2 (28.6)	*0.766*
Moderate	3 (42.9)	3 (42.9)	
Severe	1 (14.3)	2 (28.6)	
Admission to a pediatrics ward (%)	9 (90.0)	10 (90.9)	*0.943*
Days in a pediatrics ward	5 (1-9)	6 (3-10)	*0.211*
ICU admission (%)	1 (10.0)	2 (18.2)	*0.593*
Days in ICU	1 (1-1)	3.5 (2-5)	*0.667*
Total days of hospitalization	4.5 (1-10)	6 (1-15)	*0.223*

Key: ICU (Intensive Care Unit). Categorical variables are presented as frequencies (%). Numerical variables are presented as mean ± standard deviation or median (minimum-maximum). Statistically significant value if $p<0.05$.

At the beginning of the pandemic, the hospital expanded the area dedicated to the surveillance of pediatric patients in the emergency department. It implemented two circuits, one for patients with suspected or confirmed SARS-CoV-2 infection and one for other suspected conditions. This change improved the safety of families visiting the emergency department.

Additionally, local healthcare workers actively carry out opportunistic and scheduled screening for diabetes mellitus, which allowed, in many cases, the establishment of early diagnosis and the implementation of preventive measures such as lifestyle changes for children and families.

Another factor that deserves attention is health literacy on diabetes. General and specific awareness-building campaigns aimed at caregivers, teachers, educators, children, and adolescents have promoted the value of early diagnosis.

These reasons and other regional particularities cited above help explain why the number of cases of diabetes and the severity of the disease have not increased in the RAM.

Nevertheless, our study found that the POST-COVID-19 group spent a higher median number of days in a pediatrics ward or intensive care unit and that a greater proportion required hospitalization than the PRE-COVID-19 group. Although the differences were not statistically significant, they were in line with results described in other studies.[5,13]

In some cases, individuals with severe disease at the time of admission, generally with a diagnosis of severe

ketoacidosis, were hospitalized for longer and required intensive care.

In addition to the waves of COVID-19 and the corresponding public health measures implemented, there has also been a change in the seasonality of several respiratory viruses, such as Influenza, Respiratory Syncytial Virus, Rhinovirus, or Coxsackie, which may also be related to the new cases of diabetes.[12]

In 2022, a systematic review and meta-analysis found a statistically significant increase in HbA1c levels in patients newly diagnosed with DM1 during the pandemic compared to the pre-pandemic period.[14]

In this study, HbA1C levels were higher in the POST-COVID-19 group compared to the PRE-COVID-19 group (median levels of 15.3% and 11.3%, respectively), although the difference was not statistically significant.

With schools closed during the pandemic, children and adolescents were forced into a sedentary lifestyle. The eating habits of families changed. There was a fear of food shortages due to retailer understocking, the enforcement of strict confinement rules, the inability of families to buy food due to income restrictions, the increased prices charged for certain food products, and the lack of fresh foods in grocery stores. The combination of these factors caused an increase in the consumption of less expensive and readily available highly processed foods with longer shelf lives. Spending more time at home, children and adolescents started eating more between the customary regular meals.[15,16]

Family history, a factor disregarded in the references used in our study, was the only variable with a statistically significant difference between the two groups. This may demonstrate that cases of diabetic ketoacidosis diagnosed during the pandemic, some of which probably in patients who had been previously infected by SARS-CoV-2, may have a different pathophysiology in which genetic factors are less important. This difference should be investigated in other population groups to contribute to a better understanding of the pathophysiology and epigenetics of T1DM.

Considering that the region under study is an island and, therefore, somewhat of a closed environment, with an estimated population of 250,769 inhabitants (Census, 2021), family history might become more significant due to the low inherent genetic variability.

LIMITATIONS

The study presented in this article was based on an island with relatively few inhabitants and individuals with T1DM, so it does not allow for an extrapolation of the results. On the other hand, it offers a glimpse into a population that is rarely included in scientific studies.

It is a retrospective study based on the consultation of clinical records, which is always susceptible to bias.

The study considered only the described variables. It did not analyze the role of stress, diet, or environmental factors.

A new classification of diabetic ketoacidosis is available since this article was published.[17]

CONCLUSION

Family history, a factor disregarded in the references used in our study, was the only variable with a statistically significant difference between the two groups. This may demonstrate that cases of diabetic ketoacidosis diagnosed during the pandemic may have a different pathophysiology in which genetic factors are less important. This difference should be investigated in other population groups to contribute to a better understanding of the pathophysiology and epigenetics of T1DM.

T1DM is a common disease in pediatrics. Healthcare workers must be aware of the various initial symptoms of the disease and order HbA1c tests regularly when needed.

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