

Title: "Clinical and epidemiological characteristics of new-onset Diabetes Mellitus Type 1 during the COVID -19 pandemic in Children's National Health Institute, Lima -Peru"

ABSTRACT

OBJECTIVE: To describe the clinical-epidemiological characteristics of new-onset Type 1 Diabetes (T1DM) during the first two years of the COVID-19 pandemic at the National Institute of Child Health (INSN).

METHODS: Cross-sectional and retrospective study in patients under 18 years of age with new-onset T1DM and attended the INSN between March 2020 and April 2022. Data were obtained from medical records and were considered infected by SARS-CoV-2 if they had a positive RT-PCR or antigenic test in nasopharyngeal sample at the time of diagnosis. The frequency and severity were compared with institutional data for the five-year period 2015-2019. The results are shown as mean values \pm SD or minimum and maximum ranges, and in frequencies and percentages; in addition, bivariate analysis was performed for the association between T1DM and SARS Cov2 infection.

RESULTS: The cases in the two pandemic years showed an increase in contrast the previous five-year period; 69 patients debuted with T1DM (32 females); 46.4% during the first year and 53.6% during the second year; the age of most patients was between 6 and 11 years; most were pre-pubertal; 43.5% reported a time of illness of less than one month; the peaks of cases occurred in the spring months; 72.5% debuted with diabetic ketoacidosis (DKA); HbA1c was higher than 10% in 58% of patients; and, in 26.1% COVID-19 infection was demonstrated; however, due to the small number of cases, no statistical association could be established.

CONCLUSIONS: There is evidence of an increase in the number of new-onset T1DM cases compared to the five-year period prior to the COVID 19 pandemic; important peaks of cases in the spring months; high average HbA1c values at disease onset; and a very high rate of DKA compared to the pre-pandemic period.

Key words: type 1 diabetes mellitus, COVID-19 pandemic, SARS Cov2, diabetic ketoacidosis.

INTRODUCTION:

The World Health Organization (WHO), in March 2020, recognized the emerging disease Coronavirus 2019 (COVID 19), caused by Severe Acute Respiratory Syndrome (SARS-Cov-2) virus as a pandemic¹.

Viral infections have been responsible for accelerating clinical onset in susceptible people, or triggering the autoimmune process that leads to T1DM². The presence of receptors ACE2 in the pancreas, could hold the SARS-CoV-2 responsible as an etiological agent for T1DM³; thus, Nassar y col, in a systematic review on the association between COVID-19 and DM1 in patients of all ages, report a prevalence ranging from 0.15% in Wuhan to 3.0% in Francia⁴.

Experiences have been brought with regard to the behavior of the T1DM during the pandemic for COVID-19 and its association to the infection for SARS Cov2; Smith et al, report that in 29 of 184 non-diabetic patients admitted through emergency because of COVID-19 had developed persistent hyperglycemia during treatment⁵; Rabbone et al, in 53 paediatric centers, between February and April 2020 compared to 2019, find fewer new diagnoses of T1DM, but more DKA to admission⁶; Tittel et al, noting the incidence of T1DM in Germans under 18 years of age, in the period March to May 2011 to 2020, do not find greater number than the projected number of patients with T1DM debut⁷; however, Kamrath et al, also in Germany between January and June 2021, find a significant increase in the incidence of T1DM in children and adolescents, with a peak three months after the highest incidence of cases per COVID-19⁸. Likewise, Gottesman et al, at a third-level care center of complexity for children, in San Diego, California, USA (March 2020 to March 2021), see an increase in the incidence of T1DM⁹ debut; and, Kostopoulou et al report a seasonal pattern with an increasing trend of cases in spring and winter, significantly

higher HbA1c and, a higher incidence and severity of DKA during the first year of pandemic compared to pre-pandemic years¹⁰.

Diverse studies coincide, that during the pandemic for COVID 19, in children and adolescents with T1DM of recent diagnosis there has been observed an increase of cases of DKA and DKA severe^{11-16,21}; as well as systematic reviews and meta-analyses have found that in newly diagnosed children with T1DM, DKA and its severe form have increased during the pandemic¹⁷⁻²⁰. One of the reasons proposed for the DKA debut in patients with T1DM, during the COVID-19 pandemic, was the delay in seeking medical help, preceded by a longer duration of symptoms and signs of DM1; however, some studies indicate that the duration of symptoms and signs was comparable to pre-pandemic duration²²⁻²⁴; thus, even though the information provided in the studies depends on the ability of the parents to remember or to identify the symptoms and signs, delay in care would not be the only cause of an increased risk of DKA.

In our country, as far as we know, there are no previous reports on the clinical and/or epidemiologic characteristics of the patients with new onset T1DM during the pandemic for COVID-19, therefore we consider to be important to inform the **findings made by the main pediatric health center of endocrinology** in Peru.

METHODOLOGY:

Descriptive, transverse and retrospective study in which were use the files of the patients younger than 18 years with T1DM of recent beginning and that came to the INSN during March, 2020 and April, 2022; patients who had an RT-PCR test or a nasopharyngeal sample-positive antigen test at diagnosis were considered infected by SARS-CoV-2; the antecedent was not taken into account by anamnesis of COVID-19. Data on anamnesis, physical examination and laboratory results were gathered, obtaining information on age, sex, place of origin, body mass index (BMI), disease duration, glycaemia, AGA, urine ketonic bodies and hemoglobin value A1c (HbA1c); associated comorbidities and family history of DM. The frequency and severity of the onset of T1DM during the 2 years of pandemic was compared with data from the Integral

Healthcare Program for Diabetic Children (PAINDI) of the INSN Endocrinology Service of the five-year period 2015-201925.

Data were analyzed using Microsoft Excel 2010 (Microsoft Corporation, Seattle, WA, United States) and Statistical Package for Social Sciences version 22 (SPSS Inc. Chicago, IL, United States). Continuous variables are shown as mean \pm SD values or minimum and maximum ranges, and categorical variables are expressed in frequencies and percentages. In addition, the unpaired t-test was performed for continuous variables with normal distribution, the Mann-Whitney U-test for continuous variables with non-normal distribution, and the chi-squared test for categorical variables. The present study was approved by the INSN Ethics Committee.

RESULTS

During the first two years of the pandemic, compared to the previous five-year period, there was a slight to moderate percentage increase in the number of cases (11% and 28% respectively); while the increase in cases of those who debuted with DKA was more than 100% (table 1).

During the pandemic, 69 patients developed new-onset T1DM (32 women); 32 (46.4%) in the first year and 37 (53.6%) in the second; the majority of patients were between 6 and 11 years of age (65.2%); 63% they were pre pubertal; and 43.5% reported a duration of symptoms of less than one month. At onset, 50 cases (72.5%) had DKA (25 women); the HbA1c was greater than 10% in 58%; and 26.1% showed COVID-19 infection (table 2).

With regard to seasonality during the first two years of the pandemic, the distribution of cases (first/second) was: autumn (5/9); winter (8/4); spring (13/9) and summer (6/15); being October of both years, the month in which the highest number of cases of DKA were presented. Their behavior of the first and second wave of the pandemic in the first two years can be seen in Graph 1.

Pubertal development was recorded in 65 of 69 patients, the predominance was pre-puberty (63%), being more noticeable in the second year of pandemic (25/9) compared to the first year (16/15).

The differences according to the onset form (with and without DKA) are shown in table 3.

As for debut of T1DM and COVID-19, we found that the DKA presentation was more frequent in the COVID-19 negative groups and in whom the condition had not been precise. On the other hand, no differences were found in sex, age at diagnosis, HbA1c or comorbidities; but a discreet increase in the duration of symptoms before DKA onset in those with positive COVID-19 (table 4).

An association between COVID 19 and some of the variables, keeping in mind the form of debut (with or without DKA), were searched; nevertheless, there was a problem related to the sample representativeness (error Type I alpha).

DISCUSSION

In our center, during the first two years of the pandemic for COVID-19, the incidence of T1DM of new appearance, had an increase of 11 % and 28 % regarding the average of cases during 2015-2019²⁵. The reports with regard to the incidence of new cases of T1DM have been controversial; on one hand, Rabbone and col, report a lower number of patients admitted for T1DM⁶ in Italian specialized centers; Tittel and col. in a German population they do not find changes in the projected numbers of pediatric patients newly diagnosed with DM¹⁷; and, Kostopolou and col they show that the incidence of new-onset T1DM in children and adolescents did not increase during the year COVID-19¹⁰; while of another side, Unsworth and col., in specialized hospitals of London, United Kingdom, they suggest a potential increase in the number of patients with T1DM of recent beginning¹²; Kamrath and col⁸, in Germany in 2021, they find a significant increase in the incidence of T1DM⁸; and, Gottesman and cabbage, in a center of attention of third level of complexity for children, in California, the USA 2021, observe an increase in the incidence of new-onset T1DM¹⁹.

These contradictions can be explained for: a short time and number of analyzed patients who could demonstrate its association with the infection for SARS Cov2; the fear of the children's family of the possibility that they could be infected by COVID 19 in the centers of attention; and, the limited availability of medical services. In our case, the association between T1DM of recent beginning and activated COVID-19 was possible to demonstrate in 18/69 cases, nevertheless, 28/69 were negative and 23/69 were not counting with examinations, therefore it was not possible to establish association between the acute infection by SARS-Cov2 and debut of T1DM, or collateral factors and/or triggers (on a genetic base) that could unleash autoimmunity and a slow destruction of the beta cells of the pancreas and late presentation of the T1DM. The reasons; beside what was reported in the literature, which might explain the fact that we should observe an increase of cases higher to what was reported in our región²⁶, would be: the migrant population to our country that was not provided with access to the systems of health and; that our center was providing continuous attention during the whole pandemic; nevertheless, it would be necessary to wait for a national report before excluding the possibility that the increase of cases is associated with the infection by SARS Cov2, as Yang has raised it and col³.

The main characteristics observed in the patients with new-on set T1DM, during the pandemic, they were: age between 6 to 11 years without gender difference; duration of symptoms less to 1 month in 43.5 % but with 28.9 % which did not specified the beginning of the symptoms; thyroid pathology as main associated comorbidity; low association with familiar history of T1DM; HbA1c bigger than 10 % in more than half of the studied population; major number of cases in the winter months and summer for the first and second year of pandemic respectively; 72.5 % of cases making debut with DKA and mortality zero. Of these remarks, with regard to age of debut, gender, duration of symptoms, and associate comorbidity there is usually no major difference to the described thing for T1DM²⁷; regarding the high value of the HbA1c observed in our study, it is similar to the one described by Rahmati and col, where the meta-analysis find an increase of the glycaemia and HbA1c of up to 7 %¹⁸; finding that in our case might be related to the time of duration of symptoms, the not identification of the illness by the family or the providers of primary health care and the severity to the debut.

The zero mortality observed by us is also described by Nassar et al⁴ who in their systematic review show that authors such as Al Hayek or Cariou found no cases of mortality in patients with T1DM and COVID-19 or reported cases of lower risk of death in patients with T1DM, compared to other authors who report a wide variation in the mortality rate related to COVID-19, which can be explained by the clinical heterogeneity in the studied populations and the particular social situations during the lockdown.

Although we could not compare the numbers of peptide C of the patients with new-onset T1DM during the pandemic with the quinquennium pre pandemic numbers, we observe that the found average of 0.5 ng/ml is less to the one reported in the Rivero-Martín study and col, who find an average of 0.62 versus one 0.78/0.8 between the year 2020 and two previous years¹⁵, probably related to the higher incidence of DKA, also observed in our study.

The emergence of new-onset T1DM cases in our center, during the first 2 years of the COVID-19 pandemic, showed significant peaks: the first one after the first wave and the next two during and at the end of the second wave; being the two most important peaks in the months of October 2020 and 2021 (graphic 1); however, in the previous five-year period the largest number of cases had occurred at a very similar time (November); this behavior is similar to the one reported by Hawkes and col¹² during the first wave; and, Kostopolou and col¹⁰ who found an increase in winter and spring, consistent with a global seasonality pattern described by them in the period 2014-2018; assuming that there would be no relation to the epidemic waves of COVID 19.

The DKA rate in new-onset T1DM at our institution was very high (78% and 66% in the first and second year of the pandemic, respectively), compared to what has been reported in various studies; however, we were unable to establish an association with SARS Cov2 infection. In this regard, Nassar et al¹⁷, for the first year of the pandemic, show DKA rates ranging from 14.3% to 51.7%, highlighting a report in which the DKA rate in patients with COVID-19 was three times higher; Kamrath et al⁸ find a significant increase in DKA and severe DKA in children and adolescents with new -onset DM1; and, Alfayez et al¹⁸ find that the risk of DKA among patients

with newly diagnosed DM1 during COVID-19 is 44% higher compared to the to the pre- COVID-19 period.

In newly diagnosed T1DM, cases of DKA at the onset of SARS Cov2 infection and cases without ketoacidosis have been described in whom DKA occurred several weeks after apparent recovery from COVID-19; raising the question of whether SARS-CoV-2 per se or other factors would be related to the severity at the onset of the disease³. It is clear that during the pandemic there has been an increase in severity in the first form of T1DM in children and adolescents^{15,29}; although the main explanation has fallen on the lockdown (in our country, there was an almost total closure of the first level of health care during the first year of the pandemic and a subsequent prioritization of health care via telehealth than face-to-face health care) and the fear of being infected when going to health centers¹¹, difficulty in specifying the onset and duration of symptoms, lead to the suspicion of other factors involved. Furthermore, it has not been shown that the duration of symptoms and signs differ in patients with or without ketoacidosis²⁸. Thus, the explanation would be multifactorial, considering the reduction of health care services, the initial reluctance to seek medical attention, the reduction of care for other infectious or traumatic processes in which hyperglycemic states could be identified early in children with DM1, and more complex psychosocial factors ^{6,12,15,28,29}.

Regarding DKA and the age of onset of the disease, unlike other authors^{15,21,22} we found no difference between the groups, but like them, since there were not a large number of patients, it is difficult to establish a statistical significance. On the other hand, it is to be assumed that the delay in seeking medical help will be preceded by a longer duration of the symptoms of the disease; however, in our study it was not possible to demonstrate this premise due to the high percentage of debuting cases with DKA in which the onset of symptoms could not be specified. Furthermore, several studies have reported that the duration of symptoms during the pandemic was comparable to the duration before COVID-19^{13,22-24}.

Within the limitations of our study we can mention, its retrospective nature, the loss or non-collection of data, the subjectivity in the reporting of symptoms, the inability to generalize our results (due to being unaware of the situation in other health centres with different health

insurance systems), the insufficient number of cases that does not allow establishing an association between DM1 and SARS-Cov2 infection and not having evaluated psychosocial aspects related to lockdown by COVID 19.

To our knowledge, this is the first study in the country that describes clinical and epidemiological characteristics of patients with new-onset T1DM during the first two years of the COVID-19 pandemic; the results, when compared with the pre-pandemic observations at our center, provide important information to take into account in the future.

Conclusion

We observed an increase in the number of new-onset DM1 cases compared to the five-year period prior to the COVID 19 pandemic; important peaks of cases in the spring months, but with behavior similar to the pre-pandemic period; high average HbA1c values at the onset of the disease; and, a very high rate of CAD compared to the pre-pandemic period and to what is reported in the scientific literature.

Ethical aspects

This study was approved by the INSN ethics committee and the authors declare they have no conflicts of interest.

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