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Incidence of Type 1 Diabetes before and During the COVID-19 Pandemic in Isfahan, Iran

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Abstract

Background: Studies suggest a potential global increase in the incidence rate of type 1 diabetes (T1D) following the SARS-CoV-2 pandemic. This study aimed to assess the incidence of T1D in Isfahan Province before and during the pandemic to better understand the situation in this population.

Methods: In this cross-sectional study, we determined the incidence rate of new-onset T1D for the two years preceding the COVID-19 pandemic (2018-2019) and during the two years of the pandemic (2020-2021). We also calculated incidence rates each year by sex and age groups (0–4 years, 5–9 years, 10–14 years, and 15–18 years).

Results: The age-adjusted incidence rates (95% CI) of T1D in Isfahan were as follows: 16.38 (16.27-16.49) in 2018, 13.94 (13.51-14.35) in 2019, 13.17 (12.44-13.90) in 2020, and 18.09 (17.17-19.00) in 2021 per 100,000 children. The average annual percent change (APC) was 9.7%, with the highest APC of 37.34% in 2021. There was no statistically significant trend in T1D incidence during the study period ($P > 0.05$). The frequency of diabetic ketoacidosis (DKA) was higher during the COVID-19 period in 2020 and 2021 compared to 2018, with rates of 54.89% in 2021, 52.82% in 2020, 52.68% in 2019, and 32.49% in 2018 ($P < 0.005$).

Conclusion: This research observed an increasing incidence rate of T1D, particularly in the second year of the COVID-19 outbreak. While other studies have also reported an increase in T1D cases, the complex nature of T1D development makes it challenging to draw definitive conclusions about the impact of SARS-CoV-2 infection on T1D onset.

Key Words: COVID-19, Incidence, Type 1 diabetes mellitus.

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1- INTRODUCTION

Recent epidemiological data indicate a rising trend in the occurrence of type 1 diabetes (T1D), particularly in communities with lower to moderate incidence rates and in developing countries (1, 2). Beyond the genetic factors, various contributors, including viral infections, changes in gut microbiota, insufficient vitamin D levels, and increased emotional stress, are believed to play a role (3-5). Research highlights the involvement of viruses such as rotaviruses, retroviruses, enteroviruses, cytomegalovirus, Echo, Coxsackie B, and Coxsackie A in the emergence of T1D (3, 6).

In animal studies, viruses can induce autoimmune insulitis (7). Following infection with SARS-CoV-2, pro-inflammatory cytokines increase, and downregulation of the angiotensin-converting enzyme 2 (ACE-2) receptor occurs, leading to angiotensin accumulation and cellular damage. Thus, the cytokine storm is considered the main pathogenic mechanism of this virus (8). Previous reports indicate that SARS-CoV can affect the islets of Langerhans through ACE-2, potentially causing new-onset T1D (9). SARS-CoV-2 also utilizes a similar receptor on the cell surface, and since pancreatic β-cells express ACE-2, it is hypothesized that this virus may cause T1D by directly damaging the endocrine part of the pancreas. However, SARS-CoV-2 has an additional receptor, transmembrane serine protease 2 (TMPRSS2), which is only expressed in the ductal cells of the pancreas, raising questions about the possibility of direct infection of islet cells (10, 11).

During the COVID-19 pandemic, various studies have investigated the incidence rate of T1D. The results are controversial, with some studies finding no association (12-14). Some research suggests that COVID-19 infection may lead to severe clinical presentations of T1D with diabetic ketoacidosis (DKA), without significantly altering the disease's overall incidence (14). Conversely, a systematic review published in the first year of the pandemic proposed that COVID-19 infection might increase the global incidence of T1D and DKA (12). Other factors, such as lockdowns, social isolation, vitamin D deficiency, and delays in managing viral infections, could also trigger the development of T1D (15, 16). Some studies even suggest a potential global wave of T1D following the SARS-CoV-2 pandemic (17).

To clarify this association and develop preventive strategies, further studies are needed across various populations. Therefore, the present study aims to evaluate the incidence of T1D in Isfahan Province before and during the SARS-CoV-2 pandemic.

2- MATERIALS AND METHODS

2-1. Study Design and Population

The present study was conducted in Isfahan, Iran, as a sub-study of the registry for Type 1 Diabetes (T1D) in Isfahan Province. This registry involved all medical centers in the province that specialized in providing care to patients with T1D, particularly children. These centers included Imam Hussein Children's Hospital, which served as a referral center for children, as well as private clinics and offices of pediatric endocrinologists in Isfahan Province. Data were collected from diabetes clinics, referral hospitals, insurance organizations, the Hospital Information System (HIS), and the system established by the Vice-Chancellor of Health for disease registries (CIB). Imam Hossein Children's Hospital served the referral center for children with Diabetic Ketoacidosis (DKA) and new-onset T1D in the province. Therefore, it was assumed that nearly all patients with new-onset T1D in Isfahan Province during the study years were recorded.

The study was conducted as a retrospective cross-sectional study to record the number of patients under 19 years of age who were newly diagnosed with T1D, whether as outpatients or through hospitalization. Patients aged 19 years or older at the time of diagnosis were excluded. The diagnostic criteria followed the guidelines of the American Diabetes Association (ADA) (18), and all cases were classified as T1D due to the childhood onset of the disorder. Related autoantibodies were not assessed in this study. Data were also collected on the number of newly diagnosed patients with DKA and the total number of patients hospitalized with DKA at Imam Hossein Children's Hospital each year. DKA was diagnosed based on a blood glucose level of 200 mg/dL or higher, along with metabolic acidosis indicated by a low bicarbonate level. Patients referred to the center but residing outside Isfahan Province, as well as those aged 19 years or older at the time of presentation, were not included in the analysis.

The study protocol received approval from the institutional review board and regional ethics committee of Isfahan University of Medical Sciences, under research project number 1400257 and ethical code IR.MUI.MED.REC.1400.595. After obtaining written informed consent from their parents, patients were enrolled in the study.

2-2. Analytical Methods

The study presented the annual incidence of T1D in Isfahan Province from March 2018 to March 2021 per 100,000 children, calculated by dividing the number of cases by the total population aged 0-19 years. Incidence rates were reported by age group (0–4 years, 5–9 years, 10–14 years, 15–19 years) and sex. Standardized rates were computed using direct methods and national standardized population distributions published by the World Health Organization (WHO) (19). This standard population represented the expected average age distribution of the global population from 2000 to 2025. The study also reported the annual percent change (APC) for each year to identify trends over time. Additionally, the prevalence of DKA at disease onset was reported. Data were analyzed using MS Excel and the Joint Point trend analysis software (version 4.9.1.0). Quantitative variables were presented as means (SD), and qualitative variables as numbers (percentages).

3- RESULTS

The study collected data on 903 newly diagnosed cases of type 1 diabetes (T1D) in children and adolescents from March 2018 to March 2021, of which 789 were hospitalized. The mean age of the cohort was 9 years (SD = 4.2), with 51.3% being female. The study recorded 461 new-onset T1D cases during the COVID-19 pandemic. Figure 1 illustrates the annual incidence rate, while Table 1 provides details about the patient count and both crude and age-adjusted incidence rates from 2018 to 2021. There was no statistically significant increasing trend in T1D incidence over the study period, suggesting that the observed fluctuations could be attributed to chance or natural variation rather than a consistent pattern. The average annual percent change was 9.7%, with the highest APC of 37.34% occurring in 2021.

The study identified that the yearly increase in incidence was more pronounced among younger patients and females. The incidence trend showed a steeper rise in children aged 5 to 9 years, followed by those younger than 5 years. Females had a higher incidence than males across all years ($P < 0.05$). Additional information can be found in Table 2, Figure 2, and Figure 3. Throughout the study duration, Imam Hossein Children's Hospital received all patients presenting with DKA at disease onset in Isfahan. Forty-eight percent of the patients

experienced DKA at onset. The frequency of DKA cases was higher during the COVID-19 period in 2020 and 2021 compared to 2018, with rates of 54.89% in 2021, 52.82% in 2020, 52.68% in 2019, and 32.49% in 2018 (P < 0.005).

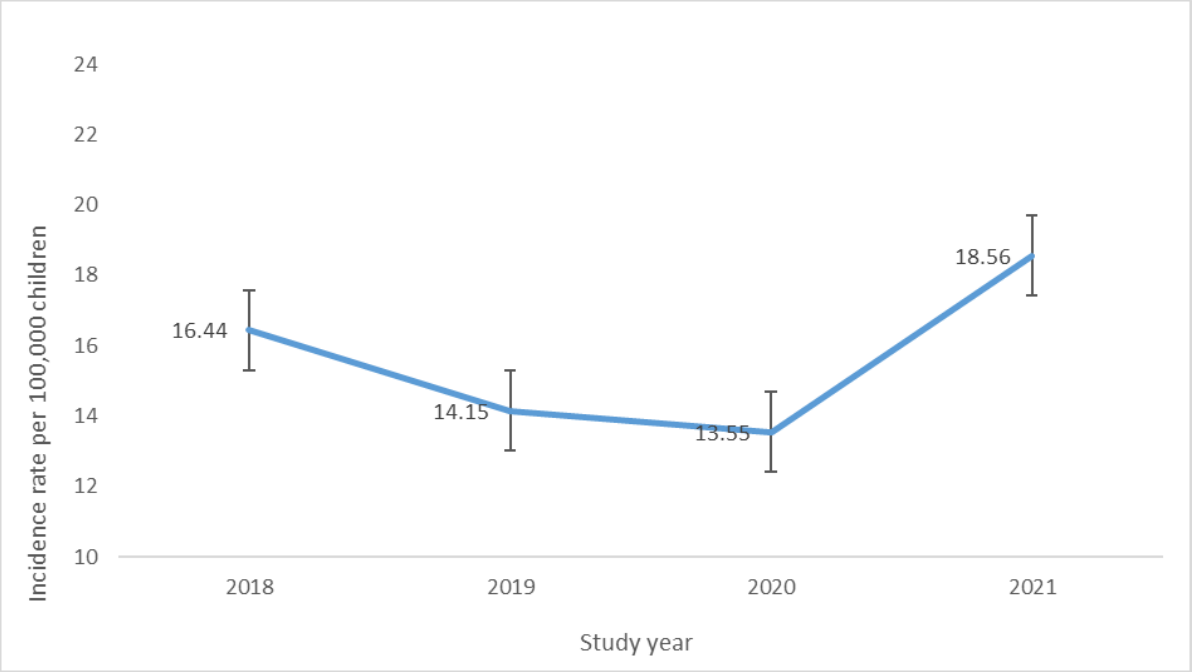

Figure-1 : Yearly incidence of T1D incidence rate in Isfahan Province form 2018 to 2021.

Table-1: Crude and adjusted annual incidence of T1D in children aged less than 19.

	2018	2019	2020	2021	p-value
Number of new cases					-
Girls	120	101	93	149	
Boys	117	104	102	117	
Total	237	205	195	266	
Population <19 yrs	1441735	1448670	1439447	1433172	-
Mean (SD) age at diagnosis	9.70±4.51	8.76±4.22	8.68±3.90	8.40±4.03	0.005
% Cases per age group					0.001
0-4	17.30	22.93	21.03	22.56	
5-9	34.18	30.73	38.97	39.47	
10-14	33.76	39.51	35.38	33.46	
15-19	14.77	06.83	4.62	4.51	
Crude incidence rate (95% CI)	16.44 (14.36 -18.52)	14.15 (12.22 - 16.08)	13.55 (11.66-15.44)	18.56 (16.34 -20.78)	0.675
Age-adjusted incidence rate (95% CI)	16.38 (16.27-16.49)	13.94 (13.51-14.35)	13.17 (12.44-13.90)	18.09 (17.17-19.00)	0.751
APC (%)	-	1.81	-5.48	37.34	-
DKA at onset (%)	32.49	52.68	52.82	54.89	<0.005

Abbreviations: APC : Annual Percent Changes, **DKA :**diabetes ketoacidosis

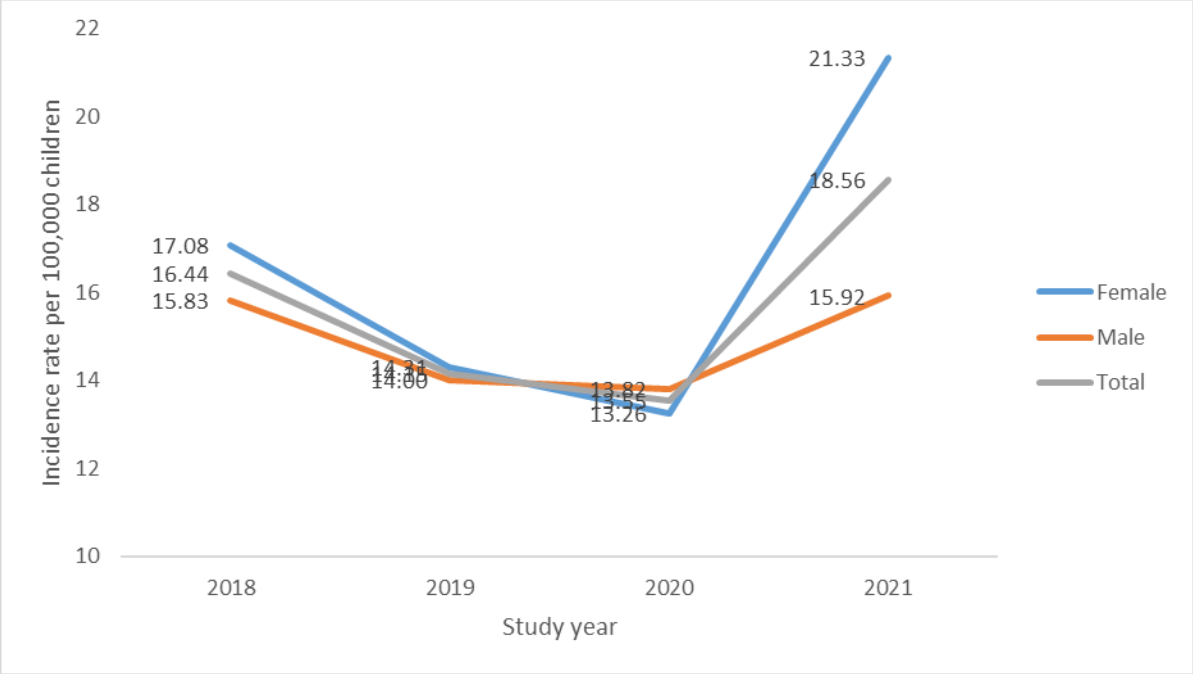

Figure-2: The incidence per 100,000 for T1D in the Isfahan population by sex groups during from 2018 to 2021.

Table-2: T1D incidence rate and 95% CI by age group and gender.

	2018	2019	2020	2021	p-value
Age groups					0.206
0–4 yrs.	10.53 (07.32 - 13.74)	12.42 (08.89 - 15.95)	11.69 (08.13 - 15.25)	18.20 (13.62 - 22.78)	
5–9 yrs.	21.09 (16.52 - 25.66)	16.21 (12.23 - 20.19)	19.11 (14.84 - 23.39)	26.13 (21.15 - 31.10)	
10–14 yrs.	23.09 (18.05 - 28.12)	22.68 (17.77 - 27.60)	18.98 (14.52 - 23.43)	24.13 (19.15 - 29.12)	
15-19 yrs.	10.88 (07.29 - 14.46)	04.31 (02.07 - 06.56)	02.75 (0.96 - 04.54)	03.60 (01.58 - 05.63)	
Gender					0.429
Female	17.08 (14.04 - 20.12)	14.31 (11.53 - 17.09)	13.26 (10.58 - 15.94)	21.33(17.93-24.74)	
male	15.83 (12.98 - 18.68)	14 (11.32 - 16.68)	13.82 (11.15 - 16.49)	15.92(13.05-18.79)	
Gender*Age group					0.741
Female					
0–4 yrs.	6.35 (2.78- 9.93)	10.31 (5.7- 14.92)	11.1 (6.14- 16.07)	22.99 (15.62- 30.36)	
5–9 yrs.	25.11 (17.97- 32.25)	17.43 (11.51- 23.34)	17.57 (11.69- 23.44)	31.73 (23.87- 39.58)	
10–14 yrs.	25.44 (17.87- 33)	23.56 (16.39- 30.74)	18.64 (12.31- 24.96)	25.6 (18.24- 32.96)	
15-19 yrs.	11.43 (6.18- 16.69)	5.06 (1.57- 8.55)	4.39 (1.15- 7.62)	2.46 (0.06- 4.86)	
Male					
0–4 yrs.	14.47 (9.23- 19.71)	14.42 (9.11- 19.74)	12.24 (7.15- 17.33)	13.63 (8.09- 19.18)	
5–9 yrs.	17.27 (11.5- 23.05)	15.05 (9.69- 20.41)	20.58 (14.39- 26.77)	20.82 (14.63- 27.02)	
10–14 yrs.	20.84 (14.16- 27.53)	21.85 (15.11- 28.58)	19.3 (13.03- 25.57)	22.74 (15.98- 29.5)	
15-19 yrs.	10.34 (5.45- 15.23)	3.61 (0.74- 6.48)	1.19 (-0.45- 2.84)	4.69 (1.46- 7.93)	

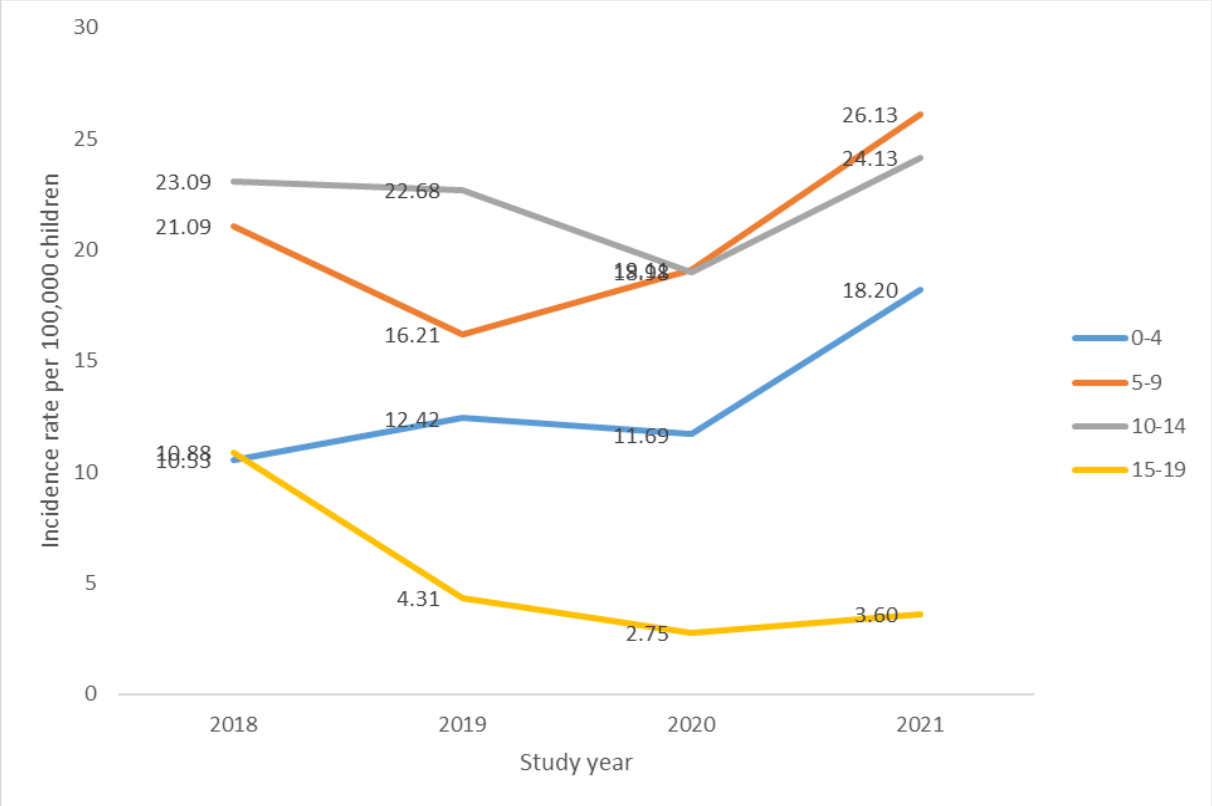

Figure-3: The Incidence per 100.000 for T1D in the Isfahan population by age groups from 2018 to 2021.

4- DISCUSSION

This study aimed to compare the incidence rates of T1D and Diabetic Ketoacidosis (DKA) presentation at onset in children under 19 years old in Isfahan Province. The findings indicated an increased incidence rate of T1D during the COVID-19 pandemic, particularly in the second year. While there was a decrease in incidence in 2019 compared to 2018, there was a subsequent increase in 2020 and 2021. The study also found a significant upward trend in incidence among females and children aged 5 to 9 years. Additionally, the frequency of DKA at onset was higher during the COVID-19 era compared to previous years. Throughout the study period, Iran experienced five waves of COVID-19, with three waves occurring in 2020 and two in 2021.

4-1. Potential Mechanisms

Several studies have examined the role of COVID-19 infection in triggering clinical T1D across different countries. However, the results lack conclusive evidence (12-14). Compared to non-COVID-19 infections, the potential role of COVID-19 in T1D development appears more pronounced (20, 21). The findings of this study did not provide sufficient support to confirm the role of SARS-CoV-2 in triggering new-onset diabetes. Beyond the infection itself, lockdowns and associated psychological issues may have contributed to T1D development (22). In Isfahan Province, lockdowns began in April 2020 and lasted for two years, potentially influencing the observed increase in 2021. It is noteworthy that COVID-19 vaccination commenced in Iran in February 2021, and during the study period, a large portion of the population had not yet been vaccinated.

4-2. Literature Review

Several studies from countries such as Italy, Saudi Arabia, and Germany did

not report a higher incidence of T1D during the COVID-19 pandemic compared to earlier periods (14, 22, 23). However, studies from the UK and Saudi Arabia suggested that while the overall T1D rate did not rise, there was an increase in cases presenting with DKA (23, 24). Other studies reported an elevated incidence rate of T1D (13, 25-28). Vorguˇcin et al. assessed the T1D incidence rate from 2017 to 2021 and identified the highest incidence in 2021 at 17.3 per 100,000, along with a higher DKA rate (42% vs. 34% during the pandemic and pre-pandemic periods) (27). Three months after the peak COVID-19 incidence, Germany's disease registry observed a notable increase in T1D cases in children, reflecting a rise during the pandemic (25).

During the COVID-19 pandemic, the Finnish Pediatric Diabetes Register (FPDR) found an increase in T1D and DKA among children and teenagers. However, this increase could not be directly attributed to SARS-CoV-2, as less than 1% of children with T1D had confirmed COVID-19 infections. It is believed that the rise in cases resulted from preventative measures like lockdowns and social distancing (29).

A meta-analysis indicated global increases of 9.5%, 25%, and 19.5% in new-onset T1D, DKA, and severe DKA, respectively, one year after the pandemic (12). However, this meta-analysis did not control for confounding factors. Another recent meta-analysis observed elevated T1D incidence across various ages and genders, with a relative risk of 1.48 (95% CI: 1.26-1.75) for new T1D diagnosis post-COVID-19 (30). Despite discrepancies regarding T1D trends during the pandemic, nearly all studies confirmed an increased incidence of DKA (31). While these studies provide insights into T1D risk after SARS-CoV-2 infection, the direct causation of new-onset diabetes by COVID-19 remains unclear.

This study identified an increased frequency of DKA among patients with new-onset T1D in the years following 2018, except for 2018 itself, where no significant difference was observed. Several studies reported elevated DKA rates among newly diagnosed T1D patients during the pandemic. A recent meta-analysis indicated a notable rise in DKA risk among newly diagnosed T1D patients amid the pandemic. These findings suggest that COVID-19 might influence T1D presentation and its potential link to DKA severity (31).

The reasons for the surge in DKA incidence remain unclear. One possibility is that the pandemic led to delays in T1D diagnosis and treatment, increasing the risk of DKA. Studies have indicated that individuals may avoid seeking medical care due to COVID-19 fears (32), which could delay T1D diagnosis and treatment, subsequently elevating DKA risk. Another possibility is that changes in T1D management during the pandemic contributed to higher DKA incidence, with some studies suggesting disruptions in insulin supply chains and medical care access might lead to suboptimal glycemic control (32).

It's important to note that these studies varied in sample size and methodology, which could account for discrepancies in findings. Further research is necessary to comprehensively understand the mechanisms underlying the increase in DKA incidence.

There is evidence suggesting that SARS-CoV-2 may accelerate the pathogenesis of T1D through both direct and indirect consequences (20). A recent study exploring potential mechanisms of T1D development following COVID-19 infection indicated various ways in which damage to β-cells can occur, including virus-induced cell death and immune-mediated loss of pancreatic β-cells. The study suggests that SARS-CoV-2 might

trigger T1D through autoimmune mechanisms such as epitope spread, molecular mimicry, and bystander activation (33).

It is proposed that the indirect autoimmune destruction of insulin-secreting beta cells caused by SARS-CoV-2, rather than direct virus-induced cytotoxicity, underlies the susceptibility to T1D. The virus seems to lead to hyperglycemia, with clinical diabetes diagnosed weeks or months after acute infection. The findings of our study could be explained by this hypothesis, as a higher incidence rate was observed during the second year of the pandemic (20).

Our study also discovered that the increased incidence was more pronounced among females and children aged 5 to 9 years. While a few studies have assessed trends by age group and supported a higher incidence in younger groups (20, 21, 25, 30), Serbia documented the highest incidence rate in children aged 10 to 14 years (27).

4-3.Gender and Age Differences

This study revealed that the increasing incidence of T1D was higher in females than in males. Some studies assessing T1D incidence rates by gender yielded conflicting findings. In Serbia and Germany, new-onset T1D was significantly more common among males than females (23, 27), while Saudi Arabia reported a higher rate of DKA in females (23). Ethnic disparities may explain these varied findings, although further research is needed to confirm this.

The underlying reasons for these differences remain uncertain. One possibility is that age and sex-specific variations in immune responses to SARS-CoV-2 infection could lead to differing risks of T1D development (34). Younger children might have less mature immune systems, making them more susceptible to T1D after viral infections (35). Another possibility is that age and sex-specific disparities in environmental factors contributing to T1D development could be exacerbated by the pandemic. Certain studies propose that exposure to specific viruses in early childhood may elevate T1D risk (36-38). Younger children could face increased exposure to such viruses during the pandemic due to heightened susceptibility to respiratory infections (36). It has been observed that females generally exhibit stronger immune responses to viral infections than males (37), potentially explaining the higher incidence of T1D among females during the pandemic. Some studies also suggest that vitamin D levels might play a pivotal role in T1D and COVID-19 development, potentially explaining the sex differences, although the exact mechanism remains unclear (39). Further research is needed to fully comprehend the mechanisms driving these age-specific differences. Understanding these age and sex-specific disparities in T1D incidence during the COVID-19 pandemic is vital for identifying those at elevated risk and for shaping preventive measures.

4-4. Interpretations of the Findings

Comparing findings across previous studies is challenging due to differences in methodology, data collection, and study duration. Our study compared the two years before the pandemic with the first two years of the pandemic, revealing a significantly increased T1D incidence rate during the second year. Howerer attributing the increasing trend solely to the pandemic is complex given T1D's multifactorial nature. The study did not assess T1D autoantibodies and COVID-19 infection indicators due to its retrospective design, necessitating further research to confirm the association between infection and T1D.

One plausible reason for the higher T1D incidence in the second year of the pandemic could be less stringent lockdown measures compared to the first year. Other

factors, such as reduced sun exposure, lack of vitamin D, stress, physiological factors, and gut microbiome imbalances, may also contribute to T1D pathogenesis (15, 20, 21).

4-5. Clinical Implications

The study's findings on T1D during the COVID-19 pandemic underscore the need for enhanced clinical practices among healthcare professionals. Increased surveillance and early detection are crucial, particularly in pediatric populations, as there has been a notable rise in T1D incidence. Implementing routine screening protocols for at-risk groups can facilitate earlier diagnosis and treatment, minimizing complications. Additionally, managing DKA requires improved education for families and providers about its early symptoms, along with clear emergency care protocols to ensure patient safety during respiratory illness surges.

Furthermore, the pandemic has highlighted the importance of psychosocial support for families managing T1D. Incorporating mental health considerations into diabetes care plans and fostering support networks can help address the psychological challenges posed by chronic conditions. The study emphasizes the necessity for further research into the connection between viral infections and T1D onset, advocating for an interdisciplinary approach among healthcare professionals. Lastly, the findings call for the development of public health policies and community outreach programs to improve access to diabetes care and education, ultimately enhancing the quality of care for children with T1D.

4-6. Limitations and Strengths

The study's strength lies in being the first of its kind in the country and covering Iran's second most significant province. However, the study has several limitations, particularly concerning potential biases from its retrospective design, which may introduce selection bias due to reliance on existing medical records. This design restricts the assessment of T1D autoantibodies and COVID-19 infection indicators. Factors such as less stringent lockdowns, reduced sun exposure, and stress could affect results, potentially leading to underreporting or misclassification of cases if patients avoided care during the pandemic. Additionally, reliance on registry data may limit the completeness of information regarding comorbidities and socioeconomic factors influencing T1D incidence. The focus on Isfahan Province further raises concerns about the generalizability of findings to other regions or countries with different healthcare systems and demographics.

5- CONCLUSION

The incidence of T1D has significantly increased, particularly in the second year of the pandemic. However, establishing a definitive link between SARS-CoV-2 infection and the onset of T1D remains complex due to the multifaceted nature of T1D pathogenesis. This study emphasizes the need for further research to investigate both direct and indirect effects of the virus on T1D, particularly in light of the increased rates of DKA observed during the pandemic. Given the chronic nature of autoimmune disease development, understanding long-term outcomes is essential. Future research should involve larger and more diverse populations with comprehensive clinical follow-ups, including assessments of C-peptide, insulin, and anti-islet antibodies, especially in pediatric patients. Additionally, thorough long-term histopathological analyses of biological samples and consideration of genetic susceptibility in individual patients are crucial for a deeper understanding of the relationship between SARS-CoV-2 and T1D.

6-CONFILCT OF INTEREST

The authors have no conflicts of interest to declare.

7-DATA AVAILABILITY

The dataset and analysis are available upon request.

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