Long-term trends of pediatric type 1 diabetes incidence in Japan: before and during the COVID-19 pandemic years (1999–2021)

Kenji Ihara (k-ihara@oita-u.ac.jp)  
Oita University Faculty of Medicine

Fumika Matsuda  
Oita University Faculty of Medicine

Tomoyo Itonaga  
Oita University Faculty of Medicine

Miwako Maeda  
Oita University Faculty of Medicine

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Abstract

Background: The incidence of type 1 diabetes has increased worldwide whereas a long-term trend for pediatric type 1 diabetes has remained elusive in Japan.

Objective: This study aimed to investigate the incidence and secular trend of pediatric type 1 diabetes before and during the COVID-19 pandemic from 1999 to 2021 in Oita Prefecture, Japan.

Subjects: We investigated the increase in numbers of newly diagnosed patients with type 1 diabetes aged <15 years from 1999 to 2021.

Method: We surveyed the medical information from hospitals in Oita and Oita Prefecture database in Japan.

Result: The incidence of type 1 diabetes in those aged <15 years increased annually by 5.3% in all children, especially by 8.1% in boys aged 10–14 years during the past 23 years. The average incidence rate of 3.9/100,000/year was almost consistent with the previous report from Asian countries. However, no significant change was found in the increasing incidence trend of type 1 diabetes before and during the COVID-19 pandemic.

Conclusion: The incidence of pediatric type 1 diabetes in Japan has significantly increased over the past 23 years, which is consistent with a worldwide trend. No significant increasing trend was observed during the past 2 years during the COVID-19 outbreak.

Introduction

Type 1 diabetes (T1D) is recognized as an autoimmune disease characterized by insulin deficiency and resultant hyperglycemia. Intensive research for T1D has rapidly increased over the past several decades, resulting in a broad understanding of many features of the disease, including its genetics, epidemiology, autoimmunity, β-cell phenotypes, and the burden of disease. The cause of T1D is known to involve both environmental and genetic factors. In addition, many reports of local or regional epidemics of T1D occurrence are best explained by environmental exposure. One of the most common triggering factors includes enteroviral infection, such as Coxsackievirus B.

T1D is classified as a polygenic disease with identical twin concordance of 30–70%, sibling risk of 6–7%, and a risk of 1–9% for children who have a parent with T1D. Ethnicity deeply contributes to the incidence of T1D; for example, Caucasians are more susceptible to T1D than African-Americans and Hispanic-Americans, whereas Asians, including Chinese, Korean or Japanese, and the people in South America were the lowest in the United States (US).

The gradual increase of incidence T1D in children <15 years has been reported worldwide. In the US, children and adolescents aged <20 years indicated a 1.8% annual increase during 2002–2012, and a
similar increase rate of 1.3% has been reported for the Canadian province of British Columbia in the period 2002–2013. In Australia, a significant increase of 1.2% (95% CI 0.4%, 2.1% was observed in the 10- to 14-year-old age group during the period 2000–2011. Within Europe, no increase was found in Sweden during the period 2005–2007, and similar flattening incidence rates were subsequently reported in two other high-incidence Scandinavian countries (Finland and Norway). Asian populations with a very low incidence of T1D (0.4–1.1 cases/year/100,000 individuals), such as Uzbekistan, Korea or China, also have increasing trends (3–12% increase). However, no remarkable increase has been reported in Japan; for example, Kawasaki et al. reported T1D incidence in patients aged 0–14 years averaging 2.37 cases/100,000/year from 1993–2001. Onda et al. also reported that T1D incidence in Japan did not increase from 2.24 (1998–2001) to 2.27 (2005–2010) cases per 100,000 persons/year. However, the results seemed elusive, partly because numbers of newly diagnosed patients might have been omitted in the registration system of “Specific Chronic Pediatric Diseases,” also called the Medical Aid Program for Chronic Pediatric Diseases of Specified Categories (MAPChD) in Japan. Since the nationwide whole-covering registration system for children with T1D has not been established in Japan, it would be difficult to estimate the national epidemiological study simply from the data of MAPChD in Japan. Alternatively, the local registry systems in each prefecture or small-scale adjacent areas would be better for extracting the epidemiological data of T1D. For instance, a recent study in Yamanashi Prefecture in Japan reported that a modest and non-significant increase was observed from 1986 to 2018 with an increasing annual rate of 1.16%; among them, the subpopulation aged 5–9 years had an annual significantly increased rate of 5.38% (CI: 2.34–8.35%).

Therefore, this present study aimed to explore the incidence, prevalence, and annual trend of childhood-onset T1D in Oita Prefecture in Japan. The chronological trends in the T1D incidence in children <15 years were carefully examined based on the medical records of three core hospitals in charge of pediatric T1D treatment in Oita Prefecture. The data from MAPChD were carefully applied to confirm the accuracy of the epidemiological data. Based on the annual trend of childhood-onset T1D, we focused on a possible change in the incidence of pediatric T1D during the COVID-19 pandemic in Japan.

**Results**

From January 1999 to December 2021, 137 children and adolescents were newly diagnosed with T1D in Oita Prefecture, Japan (Table 1). They consisted of 67 girls and 70 boys. When the patients were stratified by age at diagnosis, 40 were aged <4 years, 46 were aged 5–9 years, and 51 were aged 10–14 years. The overall incidence rate in the study period was 3.9/100,000/year. For the total cohort (aged <14 years), a significant constant increase was observed [annual percent change (APC) 5.3, 95% CI: 1.1, 9.8] (Figure 1 and Table 2). When incidences were compared between boys and girls, the age-standardized incidence rate of T1D in boys statistically increased during the 20 years (APC 6.2, 95% CI: 1.3, 11.4) (Figure S1). When incidences were stratified by sex and age groups (0–4, 5–9, and 10–14 years), the age-standardized incidence rate of T1D in boys (10–14 years old) statistically increased during the 20 years (APC 8.1, 95% CI: 3.2, 13.2). There were no statistical changes observed in girls or in other age-stratified
groups (Supp. Figure 1). A sharp increase was observed in 2007, 2013, and 2017 (7.44, 6.60, 6.60/100,000/year, respectively), but no cyclic occurrence by the stratification of 4-year intervals (1999–2002, 2003–2006, 2007–2010, 2011–2014, and 2014–2018) (Supp. Table). We analyzed the incidence of T1D in 18 municipalities in Oita, separately (14 cities, 3 towns, and 1 village), and we did not observe the regional differences during the observed period (data not shown).

This study also determined the viral infection occurrence in Oita Prefecture during the evaluation period. The surveillance data from Oita Prefecture demonstrated the prevalence of Coxsackievirus (Groups A and B) infection in Oita Prefecture seemed to be roughly synchronized with the T1D occurrence (Figure S2). In addition, we explored whether COVID-19 pandemic expansion alters the occurrence of new-onset T1D. We found that the average incidence rate (2007–2018) was 4.6/100,000/year, whereas during the pandemic years of 2019, 2020, and 2021, annual incidence rates were 6.1, 5.5, and 6.2/100,000/year, respectively, suggesting no significant change in the T1D prevalence in Oita Prefecture, Japan, before and during COVID-19 pandemic (Table 3).

Discussion

Our study demonstrated that the incidence of T1D in Oita Prefecture, Japan, has been significantly increasing every year by 5.3% during the past 23 years (1999–2021). The increasing trend of T1D incidence in Oita Prefecture was almost consistent with the previous report from Asian countries. The average incidence rate of 3.9/100,000/year in Oita Prefecture was higher than that previous report conducted in Yamanashi Prefecture (2.0/100,000/year; 1988–2016) located in the middle of Honshu Island and surrounded by mountains with a population of about 800,000 residents. The Japanese population is classified as a single race country consisted with Yayoi race of > 95% of the population, the same population size of Germany or Finland. However, T1D is recognized as a multifactorial genetic disease and therefore local and specific environmental factors play important roles in the T1D development. Our data from Oita Prefecture was slightly different from those of Yamanashi, Japan; however, the differences observed remained unknown. The environmental difference might exist between Yamanashi and Oita Prefectures might have caused the T1D development. Therefore, further studies conducted in other prefectures in Japan would be beneficial to verify our result.

In the Asian population, a report from Zhejiang province in the low-incidence region of China described a rapid annual incidence increase rate of 12.0% among those aged < 20 years from 2007 to 2013. The incidence and prevalence of childhood-onset T1D in Korea from a nation-based registry demonstrated an increase of 3–4% every year from 2007 to 2017. In Korea, the overall incidence of T1D in childhood-onset increased from 3.70% in 2008 to 4.77% in 2016, according to the Health Insurance Review and Assessment Service. The causes for this ethnicity-independent T1D increase remains unelucidated. The increase in T1D incidence rates in Korea are considerably high compared to those in other countries. Therefore, changing the populations’ genetic pool was unlikely to affect the increasing trend. However, local or regional environmental factors are may have impacted the increasing trend of pediatric T1D. The Oita Prefecture data demonstrating the Coxsackievirus infection prevalence seemed to be synchronized
with the T1D occurrence. However, it remained elusive whether epidemic Coxsackievirus infection impacted the annual increase of T1D occurrence in Oita Prefecture. Therefore, a further nationwide study is needed to evaluate the association between the occurrence of T1D and types of viral infection.

We did not find a significant change in the T1D occurrence before and during the COVID-19 pandemic. The T1D incidence in children during the COVID-19 pandemic has been reported mainly in Europe. In Poland, the incidence seemed to have decreased after the COVID-19 pandemic compared to that before the pandemic \(^{22}\). Comparatively, there was no significant change in Italy and Germany between before and after the COVID-19 pandemic \(^{23,24}\). The COVID-19 pandemic drastically changed hygiene practices, such as washing hands, wearing masks, maintaining social distance, and reducing other viral infections, especially for children; therefore, these may have caused the gradual changes in the T1D incidence. Therefore, long-term studies should be conducted to investigate the direct and indirect effects of COVID-19 infections to the development of T1D would be helpful to understand the pathogenesis and make prevention of T1D.

Our study had some limitations. First, the analyzed population size was relatively smaller than those in the previous studies in other countries. Although the numbers of pediatric T1D patients were small, the trends observed in the present study were similar to those recognized in previous studies conducted in Japan and Korea. Second, 2 years of survey during COVID-19 pandemic might be too short to conclude the results. Especially, COVID-19 infection for children has been drastically increasing since the beginning of 2022, therefore further study after 2022 will be essential to clarify the direct impact of COVID-19 infection on the development of T1D in Japanese children. Despite these limitations, we think that the present study might be relatively accurate incidences and prevalence of pediatric T1D in Japan.

In conclusion, the incidence of pediatric T1D in Oita Prefecture in Japan has significantly increased over the past 23 years, which is consistent with a worldwide trend. No significant increasing trend was observed during the past 2 years during the COVID-19 outbreak.

**Methods**

**Geographic features of Oita Prefecture.** Oita Prefecture is located on the northeast side of the coastal area of Kyushu Island. Oita Prefecture has a population of 1,124,983 (October 1, 2020) and a geographic area of 6,340 km\(^2\). Oita faces the seaside and is surrounded by mountains. It consists of 18 municipalities, including Oita City. Oita City, the capital of Oita Prefecture, is located in the east center of Oita Prefecture of the coastal area, with a population of approximately 470,000 in 2020, accounting for 40% of the prefecture's population. The population of Oita Prefecture had been steadily decreasing year by year. Children aged < 15 years and older individuals aged > 65 years account for 12.1% and 33.3% of the population, respectively. The corresponding numbers of the national average in Japan are 11.9% and 28.6%, respectively. Therefore, Oita Prefecture appears a roughly 1/100 scaled-down version of Japanese society.
**Study population.** The patients newly diagnosed with T1D, who were < 15 years of age and living in Oita Prefecture, were enrolled in this study from January 1999 to December 2021. Those who moved out from Oita Prefecture were excluded from this study.

Three strategies of data collection methods were prepared for this study. First, clinical information of newly diagnosed patients with T1D was searched from the medical records in three core hospitals: Oita University Hospital, Oita Prefectural Hospital, and National Hospital Organization Nishi-Beppu National Hospital. Second, the pediatricians in all domestic hospitals were directly asked regarding inpatient facilities for children in Oita Prefecture as follows: National Hospital Organization Nishi-Beppu Hospital, Nakatsu Municipal Hospital, Kunisaki Municipal Hospital, Bungo-Ono Municipal Hospital, Saiseikai Hita Hospital, and Tsurumi Hospital. Third, the patients were confirmed by the T1D registered in the MAPChD database. The MAPChD records in Oita Prefecture are separately stored under the management of two government offices; the Oita City Government for Oita City citizens and the Oita Prefecture for citizens of all cities and towns, except for Oita City. Since the Oita City data before 1999 and those of Oita Prefecture before 2009 were not stored, we used the Oita City data from 2000 to 2021 and those of Oita Prefecture from 2010 to 2021. The population statistics in Oita Prefecture were referred from the database of vital statistics in Oita Prefecture (https://www.pref.oita.jp/site/toukei/index-cpe.html).

**Longitudinal epidemiological data of viral infections in Oita Prefecture.** The annual occurrence of 27 types of infectious diseases, including rhinovirus, parechovirus, enterovirus, parainfluenza virus, mumps virus, adenovirus, and herpes family viruses has been investigated > 20 years in Oita Prefecture. The samples of nasopharyngeal swab fluid, feces, cerebrospinal fluid, or blood were submitted to the Oita Prefectural Research Center for Sanitation and Environment at approximately 10 fix-point medical institutions in Oita Prefecture. The epidemiological data report of viral infections in Oita Prefecture has been annually published by the Oita Prefectural Research Center for Sanitation and Environment and is available on the website (https://www.pref.oita.jp/soshiki/13002/nenpo-list.html).

**Statistical analysis.** Incidence rates were calculated by dividing the numbers of registered children by annual population estimates in Oita Prefecture, Japan. Similarly, the T1D incidence by municipality was measured by dividing the number of registered children in the municipality. Estimates of rates increase were obtained using a mixed effects Poisson regression model with age and sex as fixed effects. Time trends of age-standardized rates and annual percent change and P-values were estimated by Joinpoint analysis (Joinpoint Regression Program, Version 4.9.; Statistical Research and Applications Branch, National Cancer Institute, US). To calculate rates, the denominator values (i.e., number of boys and girls aged < 15 years) were obtained from the Japanese Model Population. Subgroup analyses were performed according to sex and age group (0–4, 5–9, and 10–14 years) in patients with T1D. The 95% CI were also calculated for proportions. All other calculations were performed using the R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria [https://www.R-project.org/]). Rates are given per 100,000 person/year. The significance level was set at 5% for two-sided tests.
The cohort is not processed when some of their records have zero counts. We aggregated the data by combining the years to eliminate the zero values according to the software operation manual. We combined the data in the smallest units. In the as-group analysis by age and sex, data binding was required up to every 5 years. Therefore, the data for 23 years was obtained, but the analysis by age and sex was for the first 20 years.

**Ethics Approval Statement**

The study was done in accordance with the Helsinki Declaration, 2004, and performed in accordance with all relevant guidelines and regulations. This study was approved by the ethics committee of Oita University Hospital, Oita, Japan (No. 2118). The study information was disclosed on the website (https://www.med.oita-u.ac.jp/hospital/kenkyu-rinri/index.html). Informed consent was obtained by an opt-out method. Patients who declared to opt out of the study excluded from this study.

**Declarations**

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**Author Contributions**

K.I. hypothesized the study. All authors collected the data. F.M. analyzed the data. K.I. and F.M. wrote the manuscript. M.M. and T.I. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed, edited, and approved the final version of the manuscript.

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**Competing interests** The authors declare no conflicts of interest in association with the present study.

**Data availability**

The data collected for the study will be available for 1 year after publication of the article upon justified request to the e-mail address of the main researcher and with a signed data access agreement.


Tables

Table 1-3 is available in the Supplemental Files section.

Figures
Figure 1

Annual trend of the age-standardized incidence rate of Type 1 Diabetes (T1D).

The annual percent change (APC) was 5.33 ($p < 0.05$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pptx
- Table2.pptx
- Table3.pptx
- SupplementaryFigure1AB2Table.pptx