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Increasing incidence of type 1 diabetes between 1986 and 2015 in Bauru, Brazil

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ABSTRACT

Aims: To assess temporal trends in the incidence of type 1 diabetes in Bauru, São Paulo State, Brazil from 1986 to 2015.
Research design and methods: The yearly incidence of type 1 diabetes (per 100,000/yr) from 1986 to 2015 was determined in children ≤14 yr of age, using individual case notification and the capture and recapture method.
Results: During thirty years (1986–2015), 302 cases were diagnosed in our population. The overall incidence was of 12.8/100,000 (95% CI: 11.2–14.4), ranging from 2.8/100,000 in 1987 to 25.6/100,000 in 2013 with a 9.1-fold variation. It was non-significantly higher in girls [13.7 (95% CI: 11.4–16.1)] than in boys [12.0 (95% CI: 9.8–14.2)] ($p = 0.48$) and significantly higher in the 5–9 yr [14.6 (95% CI: 11.8–17.4)] and 10–14 yr [15.8 (95% CI: 12.7–18.8)] age ranges compared to the 0–4 yr [8.1 (95% CI: 6.0–10.2)] age range ($p < 0.001$). The majority of diagnoses were made in colder months. The patterns of incidence were very high and high in 80.0% of the study-years.
Conclusions: The incidence of type1 diabetes in children ≤14 yr has increased in Bauru, Brazil, in the last thirty years, in approximately 3.1% annually, with an absolute crude increase of 2.5-fold. These findings pose Brazil as a country with high incidence of type 1 diabetes. All Brazilian regions should be enrolled in future studies to determine the factors that contribute to the predisposition to type 1 diabetes in our population and to the steep rise in its incidence.

1. Introduction

Type 1 diabetes (T1D) was a very rare chronic disease in the first half of the 20th century. A steep rise in its incidence has been documented in many parts of the world ever since [1]. Yearly, approximately 86,000 children are diagnosed with T1D worldwide, with an annual 3.0% increase in its incidence [2]. The highest incidence of T1D in the world is found in

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Finland (62.4/100,000/yr) [3] and the lowest in Papua New Guinea (0.08/100,000/yr) [4], with a 780-fold variation between these populations [2]. In the last decades an increase has been observed even in countries where a very low incidence rate was found previously, like China [5]. Recently, it has been found that the incidence of T1D has reached a plateau in many countries and regions with very high incidence rates such as Finland, Sardinia, Norway and Sweden [3,6–9] and in countries with an intermediate incidence such as the Czech Republic [10].

The etiology of T1D seems to be multifactorial. There must be an interplay between genetic and environmental factors that contribute to the development of T1D in a given child, in a given moment and in a given place [1]. Important differences in incidence have been reported in Caucasoid groups, even in those that are genetically similar and live in close proximity in Europe such as Finland, Sweden and Norway that have a much higher incidence than Estonia and Iceland [11–15]. Also large differences have been recently described in African countries with incidence rates varying from 1.5/100,000/yr in Tanzania to 10.1/100,000/yr in Sudan [16]. Important intra and interethnic differences in the incidence rates of T1D have also been reported in Israel between Yemenite Jews 18.5/100,000/yr compared to non-Ashkenazi Jews 7.3/100,000/yr and Arabians 2.9/100,000/yr [17]. In Italy it was also found that the incidence of T1D varies from 4.6/100.000/yr in Lombardy to 54.4/100.000/yr in Sardinia [18,19].

The estimated incidence of T1D in children and adolescents aged 0–14 yr in Bauru for the period 1986–2006 was of 27.2/100.000/yr, which placed Bauru as a city with very high risk for the development of T1D according to the World Health Organization [12]. During the study period, the incidence varied significantly from 2.8/100,000/yr in 1987 to 27.2/100,000/yr in 2002 [20].

This finding stresses the need for the evaluation of the incidence of T1D all over Brazil and in as much as possible diverse populations throughout the world in order to help the comprehension of the etiopathogenesis of T1D.

The aim of the present study was to analyze the temporal trends in incidence of T1D by age, gender, and self-reported ethnicity in children 0–14 yr in the multiethnic and highly admixed population of Bauru in the period 1986–2015, and compare the results found with similar studies conducted in other countries and regions.

2. Subjects and methods

Bauru is a city located in the southeast region of Brazil, in the geographical center of São Paulo State. It is a medium-sized city for the Brazilian patterns. It has an area of 673 km^2, an estimated population in 2015 of 366,992 inhabitants and an estimated demographic density of 545.3 people/km^2. Bauru has an altitude of 537 m above the sea level, a latitude of 22°19′ S and a longitude of 49°03′ W. It has a tropical climate with an average annual temperature of 22.6 °C. The average annual income is US$ 330.08 per person, which is considered very high for the Brazilian Human Cities Development Index [21]. The Gross Domestic Product (GDP) of Bauru is the 18th largest in São Paulo State and the 68th in Brazil. According to Brazilian Institute of Geography and Statistics (IBGE), in 2009, the GDP of the municipality was US$ 1,861,785 and the GDP per capita was US$ 5179.84 [21]. There are many sources of drinking and tap water in the city; 38% of our population is served with water having a nearly neutral pH (7.1) and 62% is served by water with a basic pH (ranging from 7.6 to 9.4) [22].

Our center has a local principal investigator who is responsible for data collection and for the supervision of all fieldwork. All endocrinologists, pediatricians, and general practitioners working in town were contacted and invited to participate in the study. All public and private schools were also enrolled in the registration process. At the beginning of every calendar school year, teachers and school coordinators receive a training class, on how to identify the signs and symptoms of diabetes and notify patients who are identified as having diabetes.

This study is a continuation of a previous study conducted in Bauru between 1986 and 2006 [20]. We extended this previous analysis in order to determine the incidence of T1D during a thirty years period, from 1986 until 2015.

The diagnosis of T1D was made in accordance with the American Diabetes Association criteria [23]. The eligible individuals had to have the diagnosis of T1D made by a doctor, the need to use insulin injections continuously before their 15th birthday, to be resident in Bauru for at least one year at the time the diagnosis was made, which was considered the day the first insulin injection was administered. Excluded patients were those with other types of diabetes such as maturity onset diabetes of the young, type 2 diabetes and secondary diabetes.

The economic status was defined according to the Brazilian Economic Classification Criteria [24].

A standard form was filled to collect patients' data that included name, address, gender, self-reported ethnicity and ancestry background, place and date of birth, date of diagnosis and socioeconomic status according to Brazilian Economic Classification criteria [20,24].

The capture-recapture method was used to estimate the degree of ascertainment and confirm the completeness of registration. This methodology allowed the estimation of the number of children with T1D by capturing them in one of the sources and recapturing them in other sources in order to minimize the probability of underestimating the real number of cases [25].

The primary data source consisted of T1D cases that were identified from records of endocrinologists, pediatricians and general practitioners. The secondary data source were those cases notified by the local diabetes association as well as school records, hospital records and any other type of communication of a new case.

Incidence rates were calculated as the incidence per calendar year per 100,000 individuals before the date of their 15th birthday. Age-adjusted incidence rates were calculated over 5-yr intervals (0–4, 5–9, and 10–14 yr). Incidence rates were classified into 5 categories: (1) very low, <1/100,000 per yr; (2) low, 1–4.99/100,000 per yr; (3) intermediate, 5–9.99/100,000 per yr; (4) high, 10–19.99/100,000 per yr; and (5) very high, ≥20/100,000 per yr.

3. Statistical analysis

Temporal trends in incidence were assessed by Poisson regression model overall, as well as stratified by gender and age-group (0–4, 5–9, and 10–14 yr). Within Poisson model, groups were compared by Wald tests. For the comparison of self-reported ethnicity proportion between the two periods of the study, and risk of having the diagnosis of T1D according to drinking and tap water pH, chi-square test was used. Odds ratios with 95% CIs were expressed as indicated. A p-value <0.05 was considered statistically significant. Statistical analysis were performed using Statistica version 13 (Dell Inc.2015).

4. Results

In the period between 1986 and 2015, 302 children ≤14 yr were diagnosed with T1D in Bauru.

The majority of these children were born locally (84.2%). Those that were not born in town (15.8%) were living here for at least one year when the diagnosis was made. Regarding self-reported ethnicity, 80.2% were Caucasians, 15.2% mulattos, 3.6% African-Brazilians and 1.0% were Native Indigenous. The ancestors of the Caucasian children were Portuguese (66.9%), Italians (42.4%), Spaniards (16.9%), Germans (4.2%) and Lebanese, Syrians, Frenchmen, Greeks, Lithuanians and Slovenians (0.5–2.0% for each group). The non-Caucasian population (19.8%) was formed by Native Indigenous, African-Brazilians or an admixture of them with people belonging to any other of the previously mentioned ethnic groups. T1D was more frequently diagnosed in children from very low and low socioeconomic classes (55.0%), followed by medium (43.0%) and high socioeconomic status (2.0%). The vast majority of diagnosed children were from the urban area 301 (99.7%). Comparing the first phase of the study (1986/2006) with the second phase (2007/2015), there was not a significant change in the socioeconomic classes in which the diagnosis of T1D was made. The same was found regarding self-reported ethnicity (82.4% Caucasians/17.6% non-Caucasians in the first phase *vs* 79.1% Caucasians/20.9% non-Caucasians in the second phase ($p = 0.5$)). Most diagnoses were made during the autumn and the winter (67.5%). The highest incidence rates were found in 2013, the coldest year in the last decade.

We have found that the majority of patients diagnosed with T1D (83.44%) lived in neighborhoods where the drinking and tap water had a basic pH (7.6 to 9.4). They had three times higher odds of having the diagnosis of T1D [OR = 3.10 (95%CI: 2.29–4.20) $p < 0{,}001$].

The incidence rates of T1D varied from 2.8/100,000 per yr in 1987 to 25.6/100,000 per yr in 2013, representing 9.1-fold variation in the incidence in the same population. The capture and recapture method was used in the years of 1990, 1995, 2000 and 2002 when one case in each one of these years was found by the secondary source and not notified by the primary one. In 2013, three cases were notified by the secondary source and not by the primary, so the estimated incidence, varied from 2.8/100,000 per yr in 1987 to 29.4/100,000 per yr in 2013, which means a 10.5-fold variation (Fig. 1). The completeness of ascertainment was of 97.7%. The overall crude incidence of T1D from 1986 to 2015 was of 12.8/100,000 (95%CI: 11.2–14.4) per yr (Table 1).

Regarding the degree of incidence rate, a low rate was found in 2 study-years (6.7%), an intermediate in 4 study-years (13.3%), a high in 22 study-years (73.3%) and a very high in 2 study-years (6.7%). Since 1997, the incidence rates have been found to be continuously high or very high.

The mean incidence of T1D was non-significantly higher in girls (13.7; 95% CI: 11.4–16.1) than in boys (12.0; 95% CI: 9,8–14.2) ($p = 0.48$) (Table 1). Even when both periods of the study were compared separately there were no significant differences between girls and boys (1986–2006 $p = 0.64$ and 2007–2015 $p = 0.19$). The male-to-female ratio was not uniformly distributed from one year to another (Fig. 2) and the crude incidence increment showed no difference between them ($p = 0.77$). The mean age at diagnosis was of 8.9 ± 3.9 yr for both genders; 8.7 ± 3.8 yr for females and 9.1 ± 3.9 yr for males. The crude incidence was significantly higher in the 10–14 yr age range, followed by the 5–9 yr and finally in the 0–4 yr ($p < 0{,}001$) (Fig. 3 and Table 1).

The estimated annual increase in the incidence of T1D in Bauru between 1986 to 2015 was of 3.1% (95%CI: 2.6–3.6), which represents an absolute crude increase of 2.5-fold. For females the annual increase was 2.7% (95%CI: 2.0–3.3) and for males was 3.6% (95%CI: 2.8–4.3). For the age groups the increase was of 1.7% (95%CI: 0.6–2.7), 2.9% (95%CI: 2.1–3.7) and 4.0% (95%CI: 3.2–4.8) for the 0–4, 5–9 and 10–14 yr age groups, respectively.

5. Discussion

The rates of incidence of T1D vary widely among countries and is increasing worldwide [1]. It seems that the incidence of T1D has reached a plateau in many countries with very high incidence rates such as Finland, Sardinia, Norway and Sweden [3,6–9], and in countries with an intermediate incidence such as the Czech Republic [10]. We have found an important rise in incidence of T1D in Bauru, São Paulo State, Brazil, over a thirty years period (1986–2015).

Data regarding the prevalence and incidence of diabetes in the Brazilian population are scarce, very limited and with a short duration follow-up [26], mostly those regarding T1D [27–28]. Aiming at filling the lack of population-based data on the incidence of T1D in Brazil, a survey was conducted in four cities located in São Paulo State, among which Bauru was included, as part of the DiaMond project [29]. After the initial data collection, three out of the four initial involved centers stopped collecting data, but we kept the notification of new cases continuously until the present moment.

Data collected between 1986 and 2006 in Bauru have already been published [20]. This registry is unique in Brazil due to its very long observation time, completeness of data, as well as the strict and continuous eligibility criteria that has been adopted across the entire period. Since 1986, we have found a steady increase in the incidence of T1D in Bauru, São Paulo, Brazil, by approximately 3.1% annually, which is basically the same 3.0% reported for the whole world [2] and also similar to the 3.0–4.0% annual increase in Europe that shows the highest prevalence rates in the world [30]. The

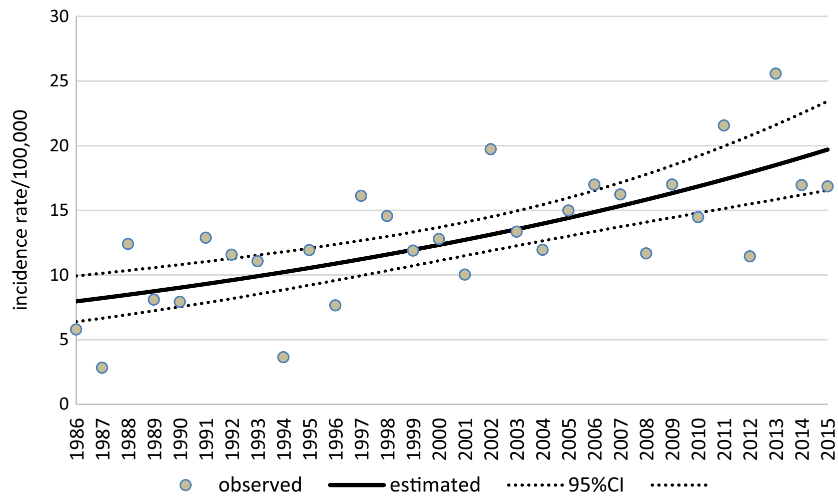

Fig. 1 – Annual incidence of type 1 diabetes in Bauru, 1986–2015.

Table 1 – Incidence rates of T1 DM by gender and age.

Gender	Incidence rates[a] (95% CI) per 100,000 person-years			
	0–4 y	5–9 y	10–14 y	0–14 y
F	9.0 (5.8–12.3)	16.7 (12.3–21.2)	15.4 (11.1–19.8)	13.7 (11.4–16.1)
M	7.3 (4.4–10.1)	12.5 (9.0–16.0)	16.1 (11.6–20.7)	12.0 (9.8–14.2)
F + M	8.1 (6.0–10.2)	14.6 (11.8–17.4)	15.8 (12.7–18.8)	12.8 (11.2–14.4)

[a] Age-standardized; population 0–14 years, Poisson model included gender, age at onset (0–4, 5–9, 10–14 y) and term for age by sex interaction as independent variables.

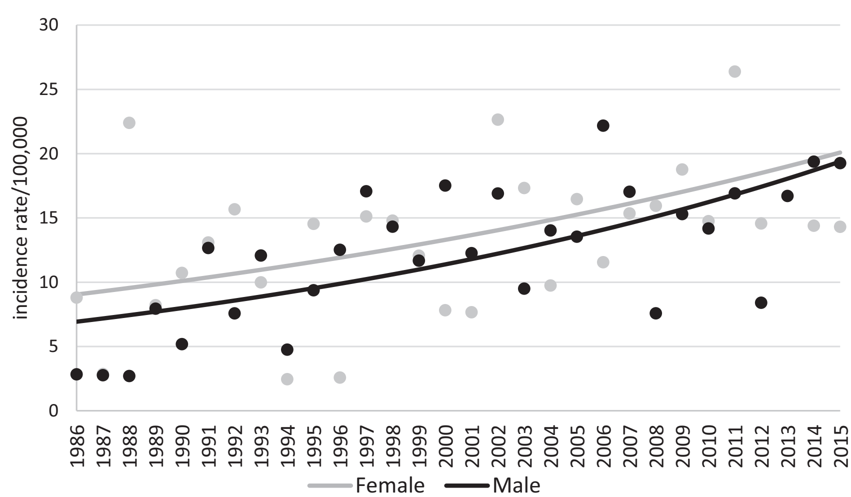

Fig. 2 – Gender-specific incidence of type 1 diabetes in Bauru, 1986–2015.

rise in the incidence of T1D we have found is not uniform, as has also been reported in other studies [31].

The majority of the diagnoses were made during colder months and in children with Caucasian ancestry as it was also found in the first phase of the study [20]. The year with the highest incidence rates (2013) had the lowest average temperature during the winter in the last fifteen years, 12.7 °C (3.9–28.8 °C) [32].

We have found no gender differences in the incidence of T1D, although a non-significantly higher incidence was found in girls than in boys. This has also been recently found in China and Turkey [31,33,34]. An excess incidence in boys has been reported in Korea and in Australia [35,36].

Another environmental factor we could evaluate was the possible role of the pH of drinking and tap water. There are two sources of drinking and tap water in town; one has nearly

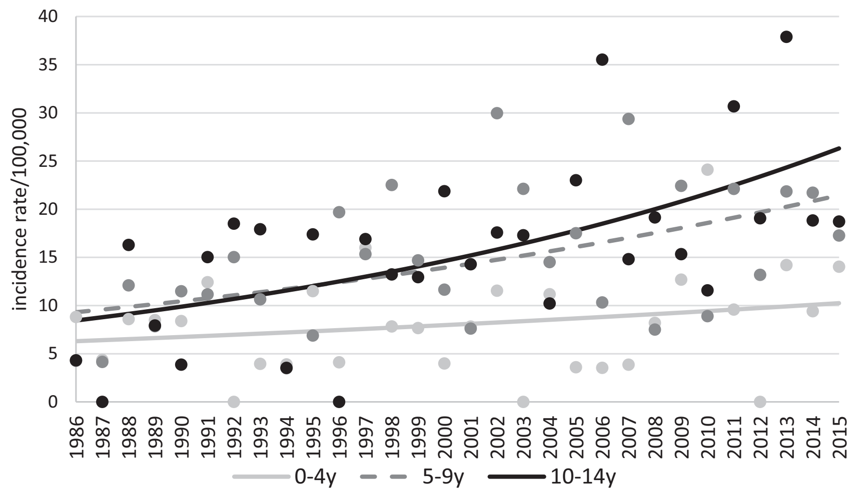

Fig. 3 – Age-specific incidence of type 1 diabetes in Bauru, 1986–2015.

neutral pH (7.1) and all the others have basic pH (ranging from 7.6 to 9.4). We have curiously found that the majority of cases (83.44%) that were diagnosed during the study period lived in neighborhoods where the drinking and tap water had a basic pH (7.6 to 9.4); this finding is not in accordance to what has been found in humans and in NOD mice [37,38].

The greatest absolute increase in incidence according to the age range was found in the 10.0–14.0 yr old group, what is in accordance with data found in Croatia and China [33,39]. Our data is in contrast with the majority of studies recently published showing a steep increase in incidence among children aged <5 yr [30,40,41].

T1D seems to be a very heterogeneous disease representing a maladaptation of some genes in a given environment. The genetic predisposition establishing the susceptibility, and the rapid changes in the environment facilitating its expressions seem to be the most probable explanation for the steep increase in the incidence of T1D worldwide [31].

Many environmental factors have been proposed as triggers in the development of T1D such as cold environment, the accelerator and the hygiene hypotheses, increased birthweight, order of birth, duration of breastfeeding, early exposure to cow's milk proteins, nitrosamines, psychological distresses, some neonatal viral infections, vitamin D deficiency, parental age, interbirth interval and maternal-fetal blood group incompatibility [7,12,13,31,42]. Recently several potential factors that could lead to a change in the gut microbiota have been related to the etiology of T1D such as gluten rich diets, highly processed foods and the use of antibiotics in the first year of life [31,37,38]. Also the pH of drinking water has been posed as a possible risk factor for the development of T1D due to its possible changes in the composition of gut microflora, that can lead to alterations in the autoimmune response as has been observed in NOD mice [37,38]. The steep increase in the incidence of T1D found worldwide cannot be explained only by genetic factors, since the genetic structure does not vary greatly over short periods of time. Environmental factors such as changes in life-style with the adoption of western dietary patterns and low physical activities would lead to weight gain, overweight and obesity in children and are surely important factors contributing to this sharp increase in T1D incidence [7,12,13,31].

As previously observed in some countries [17–19], a within-country variation in incidence of T1D has been observed in Brazil among the few studies that have been conducted with the Brazilian population. There are data from 3 other centers showing a large difference between them; São Paulo State (7.6/100,000), Londrina (12.7/100,000), and Passo Fundo (12/100,000) [27–29]. These centers are far located from each other, have different climate conditions, population densities, socioeconomic conditions, and diverse genetic backgrounds [20].

In conclusion, the overall incidence of T1D found in Bauru, that is 12.8/100,000 children aged ≤14 yr is considered to be high, placing us next to countries such as Italy, Russian Federation, France, US Virgin Islands, Serbia, India, Switzerland and Portugal [2]. Otherwise, if we consider data obtained through the application of the capture-recapture method, in 2013 we have found an estimated incidence of 29.4/100,000 per year that is considered to be very high, posing us near to countries such as Denmark, Canada and United Kingdom.

The previous studies that have been interrupted should be reassumed and further studies should be warranted in all geographic regions of Brazil to determine what is the real scenario of the incidence of T1D in the whole country, the possible genetic and environmental factors that could be involved in its development and possible ways to avoid the disease.

Authors contributions

All authors contributed equally in patients' data collection. CAN and MBG contributed equally to analyzing the data and writing the manuscript. CAN has full access to all study data and takes responsibility for the submission.

Conflict of interest statement

The authors declare they have no conflict of interest.

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