Time trends, regional variability and seasonality regarding the incidence of type 1 diabetes mellitus in Romanian children aged 0-14 years, between 1996 and 2015

Short Running Title: Type 1 diabetes incidence in Romanian children

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Ethic Committee Approval: Yes
Consent Form: No
Word count: 3,776 words
Number of figures: 2
Number of tables: 1

Grants/fellowships:
This work did not benefit from any type of financial support.

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What is already known on this topic?
The incidence of type 1 diabetes mellitus is highly variable in the world. Romania’s capital city, Bucharest, provided epidemiological data to the EURODIAB Study and the DIAMOND Project. Romania had a low incidence of the disease, but it increased continuously over a 10-year period in children aged 0-17 years.

What this study adds?
Our study found a steeper raise in the incidence of childhood type 1 diabetes mellitus than the one reported globally. Romania belongs now to the countries having a high incidence of the disease. There are significant differences between the geographic regions, and there is a seasonality regarding the diagnosis.

Abstract
Objective: The incidence of type 1 diabetes mellitus in children is highly variable in the world. The aim of our study was to analyze the evolution of the incidence of childhood type 1 diabetes in Romania between 1996 and 2015, and to search for differences amongst age groups, gender, geographic regions and month of diagnosis.

Methods: All new cases of type 1 diabetes, aged <15 years, diagnosed by two independent sources, were included in the study. The statistical methods included modeling of the incidence rates, adjusting for age groups, sex, calendar year, geographic region and seasonality.

Results: The study group was composed by 5,422 children, with overall completeness of ascertainment estimated at 93.7%. The incidence rate (per 100,000 person-years) rose continuously, from 4.7 (95% CI 3.9–5.7) in 1996 to 11.0 (95% CI 9.9 –12.2) in 2015, by a yearly rate of 5.1%, highest in the youngest and lowest in the oldest children. The mean incidence was significantly higher (p <0.0001) in Transylvania (7.9, 95% CI 7.6–8.3) than in Moldavia (6.5, 95% CI 6.2–6.9) and Muntenia (7.0, 95% CI 6.7–7.3), probably due to differences regarding ethnicity and lifestyle. The monthly incidence showed a sinusoidal pattern, peaking in January and being minimum in June.

Conclusion: The incidence of type 1 diabetes mellitus in Romanian children increased continuously during the study period by a rate that, if maintained, would lead to its doubling every 14 years. There are important differences between geographic regions and seasonality at diagnosis.

Keywords: Type 1 diabetes mellitus; Romania; children; incidence; seasonality

Introduction
Knowledge about the epidemiology of type 1 diabetes mellitus has always been of interest among diabetologists. Epidemiological information is important not only for health care systems, but also for researchers, providing valuable information about the underlying mechanisms of this chronic disease. The currently accepted theory regarding the pathogenesis of type 1 diabetes mellitus states that, in genetically predisposed individuals, the intervention of some environmental factors triggers the activation of the immune system and leads to beta cell destruction and, consequently, to absolute insulin deficiency (1). However, the mechanisms are probably more complex, as there are cases of type 1 diabetes mellitus where insulin resistance probably plays an important role (2).

Most of the data regarding the incidence of type 1 diabetes concerns children, and they derive from two important multinational studies (3, 4), as well as from national or regional reports. According to them, the incidence increases over time and is highly variable, depending on age, geographic region, and season. More specifically, type 1 diabetes mellitus is most common in children aged 10 to 14 years, has a probability of occurrence that increases with the distance from the Equator (suggesting the role of vitamin D deficiency), has its onset mainly in the cold season (underlining the role of viral infections), and increases by a mean annual rate of about 3%.

However, the knowledge regarding the secular trend of the incidence is far from being complete, since some data show continued increase (5, 6), whereas others found that the increase has leveled off (7) or has a sinusoidal pattern (8).

Romania was part of the aforementioned multinational studies, but it provided data only from the capital, Bucharest, and its surroundings. In the last two decades the Romanian Childhood Diabetes Registry was developed, and has provided information from all over the country. According to this source, Romania had a low incidence of the disease, with some regional differences (9), but it has increased continuously over a 10-year period in children aged 0 to 17 years (10).
suggests that Romania may now be included in the group of countries that have a high incidence of pediatric type 1 diabetes mellitus (11).

The aim of this paper is to characterize the evolution of the incidence of type 1 diabetes mellitus in children aged 0 to 14 years, during the 20 years that the Romanian Childhood Diabetes Registry has existed, and to establish the possible differences between various age groups and the two genders, as well as to reveal some regional and seasonal particularities.

Materials and Methods

This retrospective study was conducted on Romanian boys and girls under the age of 15, diagnosed with type 1 diabetes mellitus between 1996 and 2015. It was approved by the Ethical Committee of “Victor Babes” University of Medicine and Pharmacy Timisoara (approval number 43/11.05.2016). Due to the fact that it was a retrospective, epidemiological study, informed consent was not requested. The cases were gathered from two independent sources. The primary source was the Romanian Childhood Diabetes Registry. This registry was started in 1996 by ONROCAd (Romanian acronym for the “Romanian National Organization for the Protection of Children and Adolescents with Diabetes”), and revised on a yearly basis, relying on the reports of the physicians which were managing these cases. Romania is divided into 41 administrative districts. For children with diabetes mellitus, the medical assistance is provided in a centralized manner. According to the rules imposed by the National Health Insurance Company, insulin and glucose strips are reimbursed only if prescribed by a limited number of physicians, up to 4 in each district (upon case, this could be a pediatrician, a diabetologist or an endocrinologist). Consequently, the primary source was based on the yearly reports of about 70 health care professionals, and it includes children with type 1 diabetes mellitus (the majority of the cases), as well as with other types of diabetes: type 2, monogenic, and related to different conditions. The secondary source was represented by the records of the “Cristian Serban” Medical Center in Buzias, a public healthcare center specialized in the diagnosis, evaluation, education and treatment of children and young people suffering from diabetes mellitus from all over the country, considered a European Reference Center for the management of pediatric diabetes (12).

The completeness of ascertainment of the cases was calculated using the capture-recapture method (13), using the number of patients diagnosed by each of these two sources to estimate the number of missing patients and the total number of children.

The diagnosis of type 1 diabetes mellitus was established by the lead physician on each case, based on the internationally accepted guidelines (14). The date of onset of the disease was considered to be the date of the first insulin injection. Cases that were less than 6 months old at diagnosis were excluded, since the probability of developing type 1 diabetes mellitus before this age is very low.

The demographic data was retrieved from the National Institute of Statistics (15). They derived from the censuses performed in 1992, 2002, and 2011, as well as from the estimates for the rest of the years. The data was collected for each of the 41 administrative districts, for both genders, and for the 3 standard age groups: 0-4 years, 5-9 years, and 10-14 years.

The incidence rates were expressed as new cases per 100,000 person-years at risk, with approximate 95% Poisson confidence intervals. Poisson regression was used to model the incidence rates, adjusting for age groups, sex, calendar year, and geographical region, taking the respective background population into account as exposure.

The analysis of seasonality at diagnosis was based on all cases aggregated over sexes and all years, with stratification by age at diagnosis (0-4 years, 5-9 years, 10-14 years), as well as all ages combined. Following Edwards (16), the analysis included a general test for seasonal variation (“Total”, 11 degrees of freedom (df)), a test for sinusoidal variation (“Cyc. trend”), as well as a test for seasonal variation unexplained by lack of fit of the sinusoidal model (“Residual”, 9 df).

Results

Completeness of ascertainment

After the exclusion of the other types of diabetes mellitus, the primary source (the Romanian Childhood Diabetes Registry) identified 5,248 cases, whereas the secondary source (the medical records from the “Cristian Serban” Medical Center in Buzias) provided 1,878 cases. Among the total 5,422 cases ascertained, 1,704 were captured independently by both sources. Based on this data, the total number of patients captured by the two sources was 5,422, the number of missed cases was estimated to be 362, and the probable total number of patients was 5,784.
The overall completeness of ascertainment was 93.7% (95% CI 93.1–94.4) and constant during the study period (data not shown). The value of the completeness of ascertainment for the primary source was 90.7% (95% CI 89.4–92.1), and for the secondary source 32.5% (95% CI 31.2–33.7).

Trends in the incidence of type 1 diabetes mellitus between 1996 and 2015

The yearly incidence rate (per 100,000 person-years) showed a continuous increase during the study period, from 4.7 (95% CI 3.9–5.7) in 1996 to 11.0 (95% CI 9.9–12.2) in 2015 (Table 1), corresponding to an annual mean increase of 5.1% (95% CI 4.6–5.6). This phenomenon was due to the absolute increase in the number of new cases of type 1 diabetes mellitus, as well as to the decrease in the target population. The rise of incidence was encountered in all age groups, reaching peak values in the youngest children (annual rate 7.6% (95% CI 6.3–8.9)), and the lowest values in children aged 10-14 years (annual rate 3.9% (95% CI 3.1–5.8)). The increasing trend characterized both boys and girls, without significant differences between them, and it was present in all the geographic regions of the country.

The mean incidence of the disease in the study period was 7.2 (95% CI 7.0–7.4). It was not significantly (p=0.53) higher in boys (7.3, 95% CI 7.0–7.5) than in girls (7.1, 95% CI 6.9–7.4). The differences between the age groups were statistically significant (p <0.0001). The highest incidence was found in the age group 10-14 years (9.1, 95% CI 8.7–9.4), followed by the age groups 5-9 years (7.6, 95% CI 7.3–8.0), and 0-4 years (4.5, 95% CI 4.2–4.7). The mean age at diagnosis was similar in girls and in boys (p=0.81).

Regional differences in the incidence of type 1 diabetes

There were striking differences between the geographic regions regarding the incidence of type 1 diabetes mellitus (Figure 1). The mean incidence during the study was significantly higher (p <0.0001) in Transylvania (7.9, 95% CI 7.6–8.3), in comparison to Moldavia (6.5, 95% CI 6.2–6.9) and Muntenia (7.0, 95% CI 6.7–7.3).

Seasonal variation in the incidence of type 1 diabetes mellitus

The incidence of type 1 diabetes mellitus differed by months in a pattern compatible with a sinusoidal variation (Figure 2). The incidence was higher during the cold season, with the maximum value registered in January, and lower values during the warm season, with the minimum value encountered in June. The pattern of seasonal variation was significant (p <0.001) for all age groups except for the youngest (0-4 years), however with statistically significant evidence of residual variability.

Discussion

The epidemiology of type 1 diabetes mellitus in Romanian children has been described previously. The first papers included only the capital, Bucharest (17), this region being part of the two important international epidemiological studies, EURODIAB (4) and DIAMOND (3). Later, data covering the whole country also became available (9, 10). The present update is justified by the enlarged study material, now covering a full 20-years period from 1996, by the need to confirm the previously published age, gender and calendar time trends, and by the necessity to address the geographical distribution within Romania and the seasonality at diagnosis.

Completeness of ascertainment

The incident cases were retrieved from two sources that diagnose and report new cases of childhood type 1 diabetes mellitus independently from each other. The primary source was the Romanian Childhood Diabetes Registry, where children with diabetes are included based on the evidence kept and forwarded by local diabetologists or endocrinologists, and the secondary source was represented by the data files of the patients admitted to the “Cristian Serban” Medical Center in Buzias, a public hospital where children with diabetes mellitus are admitted if referred by a physician or by direct registration via the diabetes association or website. The overall completeness of ascertainment was high (93.7%), and it was constant over the study period. The primary source had, by itself, a high completeness of ascertainment (90.7%). This could be explained by the fact that the assistance of the children with diabetes mellitus is provided by a medical system that can be considered centralized, as each of the 41 districts includes only few physicians (up to 4) who are in charge of these cases. The relatively low number of physicians facilitates the achievement of almost complete data for the Romanian Childhood Diabetes Registry. The low completeness of ascertainment of the “Cristian Serban” Medical Center in Buzias may be explained by the fact that only a small percentage (about 30%) of all the children with diabetes from Romania benefited from evaluation, education and treatment within this hospital.
Trends in the incidence of type 1 diabetes mellitus between 1996 and 2015

During the 20 years of follow-up, the incidence of type 1 diabetes mellitus in children increased constantly, with an annual rate of 5.1%, which is higher than the one reported by the EURODIAB study and the DIAMOND project (3, 4). Due to the high completeness of ascertainment, constant across the study period, one can consider this information accurate and exclude bias due to under-reporting. In the past, Romania belonged to the group of countries with a low incidence of type 1 diabetes mellitus in children (9), but, as shown by the present data, the country presently has a high incidence of this disease.

The rapid increase in incidence rates usually characterizes countries with lower overall incidence (18), while in those where the disease is more prevalent, the incidence rate increases slower or even levels off (6, 7). However, in Romania, the increase continued to be steep even when the incidence became high, and, if this rate will be maintained, one can expect a doubling of the incidence rate every 14 years. Even without valid information, one can speculate that, in the past, the incidence rate of type 1 diabetes mellitus was approximately constant, probably at a low value, and at a certain moment it started to increase (19). That specific moment was probably shortly after 1990, when the political changes in Romania led to important changes in lifestyle, represented by a more intense migration and by the increased use of industrially processed food. These might have led to a more intense exposure to infectious agents and to chemical substances found in food, putative triggers for the autoimmune destruction of the beta cells. It is very probable that the different environmental factors contributed to the marked increase in the incidence of type 1 diabetes mellitus, as the study period is too short for the occurrence of genetic changes that could explain the rise in the incidence. The economic development was considered the reason for this rapid increase in the incidence of type 1 diabetes mellitus by other authors, as well (20).

It is known that Hungary (21) and Germany (22) have higher incidences of childhood type 1 diabetes mellitus compared to Romania. One can assume that the Hungarian and German ethnicities in Romania (two of the most important ethnic minorities), who have a similar genetic background to the population from the aforementioned countries, might have higher incidences of type 1 diabetes mellitus and that an increase in the percentage of those ethnicities might explain the raise in the incidence of type 1 diabetes. However, this demographic phenomenon was not shown by the national censuses (15), which demonstrated, in fact, a decrease in the percentage of these populations, as a consequence of their emigration to Hungary and Germany, respectively.

Another possible explanation for this steep increase is the shift to a younger age at diagnosis. This theory states that type 1 diabetes mellitus occurs at a younger age, due to an earlier intervention of the environmental triggers, and that the overall incidence of the disease is not changed. The hypothesis is supported by several trials that have analyzed the evolution of the incidence of type 1 diabetes mellitus in children, as well as in adults (23), and was suggested by previous work carried out by our group, in which the analysis performed over a 10-year period noticed an increase in the incidence of type 1 diabetes in the age groups 0-4, 5-9 and 10-14, and a decrease in the age group 15-17 (10). In the present study, the more rapid increase in the incidence of type 1 diabetes mellitus in the youngest children may be an argument to support the theory of the shift towards a younger age at diagnosis. The highest incidence of type 1 diabetes was registered in the age group 10-14. This is the age when most of the children reach puberty, and the insulin resistance induced by the release of sex hormones may play an important role in the onset of type 1 diabetes (2). Boys had higher incidences of type 1 diabetes mellitus in most years and for all age subgroups. This is usually the case for populations with high incidence of the disease (24), without a clear explanation for this phenomenon. The mean age at diagnosis was significantly lower in girls as compared to boys. It is known that girls usually reach puberty at a younger age in comparison to boys, and this might be an explanation for the earlier onset. Our data are in concordance to the reports of other authors regarding this aspect (25).

Regional differences in the incidence of type 1 diabetes

Romania is composed of three geographic regions (Transylvania, Moldavia, and Muntenia), each of them including several administrative districts. Transylvania was, in the past, part of the Austro-Hungarian Empire. Nowadays, its population is more heterogeneous, as compared to Moldavia and Muntenia, the Hungarian and German ethnic minorities being more numerous here than in the other regions.
Our study has revealed significant differences between these three regions. The highest mean incidence was encountered in Transylvania, and this was significantly higher compared to Moldavia and Muntenia, respectively. In a previous paper published by our group (9), an analysis performed on these three geographic regions, between 1992-1995, showed similar differences, though the mean incidences were much lower. The main explanation for this finding might be the ethnic heterogeneity of Transylvania, knowing that children from Hungary and Germany (who have a genetic background similar to the aforementioned minorities from our country) have higher incidences of type 1 diabetes in comparison to Romania (21, 22). However, we cannot test this hypothesis further since neither the primary nor the secondary source contains information about the ethnicity of the patients. Another possible explanation could be the fact that Transylvania is a region with a higher standard of life, compared to the other two regions, and, consequently, one may speculate that its population has a higher mobility (more frequent trips in different regions of the world), and adhered in a higher proportion to the modern eating habits, based on industrial processed food. These differences could facilitate the interaction of some environmental factors (infections, food antigens) in a genetically predisposed population, and trigger the autoimmune destruction of beta cells.

Seasonal variation in the incidence of type 1 diabetes mellitus

The seasonal variability of type 1 diabetes underlines the role of infectious triggers and of the deficit of sun exposure in the pathogenesis of the disease (26, 27). The putative infectious agents, notably viruses, are more common and long-lived in winter; consequently, given their involvement in the pathogenesis, the number of new cases should be higher in the cold season. In addition, the reduced number of sunny days in the winter induces a deficit in the subcutaneous synthesis of vitamin D, known to have an important role in immune modulation (28). However, due to the fact that the time elapsed between the intervention of the trigger and the onset of hyperglycemia is highly variable, the seasonal variability is not always obvious.

Our study has revealed significant seasonal variation of the incidence of type 1 diabetes, the highest values being recorded during the cold season (maximum incidence in January), and the lowest during the warm season (minimum incidence in June). This pattern was seen in children belonging to the age groups 5-9 and 10-14, but not for the youngest ones. The quite constant occurrence of the disease between ages 0-4 could be explained by the decreased exposure to infections, due to country’s specifics: children are raised by their parents in the first 2 years of life (this is the length of the parental leave), by their grandparents in the next year, and the admission in communities, where the infections are more prevalent, usually takes place after the age of 3 years.

Similar data was reported by the EURODIAB investigators (27) for the majority of the 23 member centers, except for two amongst which Romania’s capital, Bucharest. Since our study periods overlap substantially (1989-2008 in EURODIAB and 1996-2015 in our study) and the meteorological conditions do not differ significantly in Bucharest from the rest of the country, the different results could be explained by a lower prevalence of vitamin D deficiency in Bucharest, possibly due to better preventive measures.

Our study has several limitations and strengths. The main limitations are represented by the lack of information regarding the ethnicity of the newly diagnosed patients (that could have facilitated the interpretation of the regional differences in the incidence), the absence of data about the dietary habits in early life and of the population from different geographic regions, as well as the lack of evidence about the evolution of the incidence of diabetes mellitus in adolescents and young adults (that could have supported the theory of the shift towards a younger age at diagnosis). The strengths of our research consist in the existence of accurate data, provided by two high quality sources that cover the entire territory of the country during a long period of time.

In summary, we have analyzed the trends in the evolution of the incidence of type 1 diabetes mellitus in Romanian children aged 0-14 years, over a 20 year span (1996-2015), considering, as well, some particularities regarding age group, gender, geographic region, and seasonality. We found a steeper raise in the incidence than the one reported globally, for both genders and all age groups, and, if this trend is maintained, it would lead to a doubling of the incidence every 14 years. Romania belongs now to the group of countries with a high incidence of childhood type 1 diabetes mellitus. There are significant differences between the geographic regions, and there is a seasonality regarding the diagnosis of type 1 diabetes mellitus that concerns all age groups, except for the youngest one. The shortcomings of the research could be surpassed by the continuation of the follow-up, and the addition
of new information about adult patients, ethnicity of the subjects, and lifestyle (particularly eating habits).

Acknowledgements
The authors acknowledge the contribution of the ONROCAD Study Group to the setup of the Romanian Childhood Diabetes Registry. The most recent structure of the group is as follows: Mihaela Antohi, Rodica Avram, Simona Berbece, Mihaela Bica, Claudia Bolba, Liliana Buta, Marta Bzduch, Mihaela Camenita, Nicoleta Chitea, Silviana Constantinescu, Adriana Cosmescu, Victoria Cret, Gabriela Creteanu, Ruxandra Dinca, Larisa Dumbrava, Iulia Dunca, Georgiana Enache, Gabriela Fetecau, Mariana Ghenof, Cristian Guja, Gabriela Ichim, Sorin Ioacara, Ildiko Kicsi-Mat Yus, Eletka Koos, Csaba Lorinczi, Monica Marazan, Raluca Memu, Cristina Mihai, Mihaela Mihu, Anelia Minesscu, Livia Moldovan, Maria Mota, Diana Musat, Aurel Nechita, Anca Nicoara, Carmen Novae, Nicoleta Oarga, Carmen Oltean, Eva Pahon tu, Margareta Peter, Ioan Petrescu, Ella Pintulei, Lucretia Pircalaboiu, Lavinia Pop, Amorin Popa, Gelu Popescu, Sena Popescu, Catalina Porojnicu, Ana Pricope, Ileana Puiu, Stanca Raceala Motoc, Gina Scutaru, Cristian Serafinceanu, Viorel Serban, Alexandra Sima, Ana Maria Tanasie, Bogdan Timar, Romulus Timar, Adriana Tutescu, Margit Vargancsik, Iulian Velea, Adrian Vlad, Mihaela Vlad, Virgil Vlasceanu, Daniela Zaharie.

Authorship contribution
Conception of the study: Adrian Vlad, Viorel Serban
Design of the study: Mihaela Vlad, Bogdan Timar
Data collection: Adrian Vlad, Mihaela Vlad, Bogdan Timar, Alexandra Sima
Analysis and interpretation of the data: Adrian Vlad, Anders Green, Sören Möller
Literature research: Viorel Serban, Mihaela Vlad, Bogdan Timar, Alexandra Sima
Writing of the text: Adrian Vlad, Anders Green, Sören Möller

References
Table 1. Crude incidence rates for type 1 diabetes mellitus in Romanian children aged 0-14 years, between 1996 and 2015

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Figure Legends

Figure 1. Regional differences in the incidence of type 1 diabetes mellitus in Romanian children aged 0-14 years, in the period 1996-2015
Figure 2. Seasonality of the incidence of type 1 diabetes mellitus in Romanian children aged 0-14 years (1996-2015)
For each age group $\chi^2$-values with corresponding degrees of freedom (df) and p-values are presented as Total (test of heterogeneity by month), Cyc. trend (significance of accepting a sinusoidal model), and Residual (test of variation unexplained by the sinusoidal model)