ORIGINAL RESEARCH

# Epidemiological features of New-Onset Type 1 Diabetes Mellitus in children and adolescent during 2010-2014 in Albania - a unique experience.

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## Abstract

**Aim:** Diabetes mellitus is a major public health problem worldwide. Type 1 diabetes mellitus (T1DM) is the most common metabolic chronic disease in genetically susceptible children and adolescents, due to an autoimmune process characterized by a selective destruction of insulin producing β-cells. The aim is to assess the epidemiological features of new-onset T1DM in children and adolescent at the national level during the period 2010-2014 in Department of Pediatrics, Endocrine Unit, University Hospital Center 'Mother Teresa', Tirana, as the unique center for pediatric endocrinology and diabetology in Albania.

**Methods:** The clinical and laboratory characteristics of 152 patients aged <15 years newly diagnosed with T1D from 1 January 2010 to 31 December 2014 were studied. T1D was diagnosed according to WHO 2006 criteria and DKA was diagnosed based on ISPAD 2014 criteria. Patients were classified into 3 sub-groups (I: 0-4 years, II: 5-9 years, and III; 10-14 years). Statistical analysis was performed using SPSS 26.

**Results:** The incidence of new-onset of T1DM was 5.012/100.000/year. The mean age of children at diagnosis was 8.3 ± 3.6 years. The patients were mostly diagnosed at ages 5-9 years (40.1%), and 10-14 years (39.5%), followed by the 0-4 years age group (20.4%). Mean duration of symptoms was 23.35 ± 17.16 days; longer in the subgroup 5-9 years (P= 0. 0.013). Three quarters (75%) of children with T1DM live in urban areas. Viral infections or other circumstance triggers were in 41.9% of children aged 0-4 years compared to other subgroups (P=0.002). Most of the children were born in the spring−summer months (53.23%) compared to the autumn−winter months (46.77%). Approximately 1/4 of the children were born and diagnosed with type 1 diabetes in each of the seasons of the year and 52.63% of the patients studied were first born. Family history for DMT1 and DMT2 is observed in 15.8% and 17.8% of the children, respectively. Polyuria (99.3%), polydipsia (99.6%) and weight loss (98.1%) were the most common symptoms and 67.8% of patients presented with diabetic ketoacidosis (DKA). Misdiagnosis was in 21 (13.8%) patients. Mean glycosylated hemoglobin A1c (HbA1c) was 11.63%; 11.9 ± 2.0 in DKA positive children and 11.1 ± 2.4 in DKA negative children (p= 0.195).
At diagnosis and during follow up of T1DM 25% (38/152) developed associated autoimmune diseases; 68.42% at diagnosis of T1DM and 65.79% (25/38) of patients were female. During follow up children with T1DM developed associated CD and SAT, 2.54, and 2.19 years, respectively.

**Conclusion:** Diabetes mellitus is one of the major public health problems worldwide. Albania is a country with middle incidence of T1DM and the age at onset is decreasing. The symptoms lasted significantly longer and mean HbA1c levels were significantly higher in older children. The incidence of DKA in children with newly diagnosed T1DM is high.


***Keywords:*** *autoantibodies, children, diabetic ketoacidosis, incidence, seasons, type 1 diabetes.*

**Conflicts of interest:** None declared.

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## Introduction

Type 1 diabetes mellitus (T1DM) is the most common endocrine and metabolic disease in children and adolescents aged 0–14 years (1). T1DM represents 5-15% of the diabetic population; 85-95% have T2DM and less than 2% have other forms of diabetes (2). The incidence of childhood type 1 diabetes is increased worldwide more than two to three folds during the last decades, particularly in Finland and Sardinia ("Hot Spots" of the world) (3).

The incidence of T1D in children < 15 years of age is increasing significantly, approximately 3% (range 2-5%) (1,4,5). From 1965 to 2012 the incidence of type 1 diabetes in pediatric population has increased significantly from 9.44% (8.22–10.66) to 19.58% (14.55–24.60) (6), with the exception of Central America and the West India (4). The overall incidence of DMT1 is 11.43/100,000/year, and according to gender; 11.42 (10.23–12.61) in boys and 11.11 (9.94–12.27) in girls (4). In many European countries the overall incidence has increased to 3.9% (ranges from 0.6% - 9.3%); the increase is higher in children aged 0-4 years with 5.4%, compared to 4.3% and 2.9% for age groups 5-9 and 10-14, respectively (4).

The main epidemiological characteristics of type 1 diabetes in children < 15 years old are: the large variation of incidence from 0.1 in Venezuela to 62.3 per 100,000 per year in Finland (7); the increasing incidence in countries with lower incidence and the trend of occurrence towards the younger age group (0-4 years) (3). Variation of type 1 diabetes incidence cannot be explained by genetic factors alone (frequency of protective HLA-DQ alleles between populations) suggests the importance of environmental factors in the complex pathogenesis of DMT1.

Exposure to one or more environmental factors of genetically predisposed individuals, triggers an immune response that causes the selective destruction of pancreatic beta cells. Among environment factors include: latitude and geographic position (8-11); frequent and high exposure to cow's milk and its products (12), consumption of foods high in carbohydrates (13); short-time exposure to ultraviolet radiation and insufficiency and deficiency of vitamin D; oceanic climate (cold winter and summer) (6); prenatal and postnatal viral infections (14-16); pregnancy-related factors (parental age at birth, order of birth, maternal illness, viral infections) and perinatal period (birth weight, gestational age) (17); use of pharmaceutical products (antibiotics); obesity (increased BMI) (18-20); migration; socio-economic status with high income (7); gender and age (21) as well as the month and season of birth (22) are all associated with increased risk of type 1 diabetes.

This study aims to investigate the epidemiological features of T1DM in children and adolescents aged <15 years, during the period 2010-2014 in Albania.

## Patients and methods

### *Study type*

This study represents a series of patients (cases) newly diagnosed with type 1 diabetes mellitus presented at the Specialty Service, Endocrinology Clinic, "Mother Teresa" University Hospital Center, Tirana (QSUT), during the period 2010-2014.

### *Study population*

This prospective study from January 1, 2010 to December 31, 2014, included 152 patients who met the criteria: children diagnosed with T1D for the first time < 15 years old in Albania. The number of children and adolescents aged 0-14 years old from 2010-2014 according to INSTAT is 3,032,819 children (1,451,992 females and 1,580,827 males). Patients are classified into 3 age

groups (I: 0-4 years, II: 5-9 years, and III: 10-14 years).

**Inclusion criteria**: the study included 1) new cases aged < 15 years diagnosed for the first time with diabetes mellitus type 1 during the period January 2010 - December 2014 resident in Albania, which from a geographical point of view corresponds to the administrative borders and census; 2) individuals who received their first insulin injection before their 15th birthday and resident in Albania at the time of the first insulin administration.
**Exclusion criteria**: new cases ≥ 15 years of age during the period 2010-2014, cases of diabetes mellitus from secondary causes as a result of a primary pathology (cystic fibrosis, corticotherapy, MODY, etc.) were excluded from the study.

***Data collection***
Data for this study were collected prospectively using a standardized clinical record. Information was collected on a range of demographic and laboratory data.
The epidemiological data regarding the date of birth, the date of initial presentation of T1DM and age at diagnosis, the order of birth, the birth weight, the mode of delivery, and pubertal status were obtained from the patients' clinical records. The diagnosis of T1D was determined according to WHO, 2006 criteria; the ISPAD, 2014 criteria were used to determine DKA; hyperglycemia (glycemia> 200 mg/dL or > 11 mmol/L), metabolic acidosis (pH < 7.30, and /or plasma bicarbonate level < 15 mmol/L or ketones in urine (ketonuria > 2+), accompanied by history of polyuria, polydipsia, nocturia, weight loss, dehydration, nausea, vomiting, abdominal pain, respiratory signs (acetone odor, respiratory distress, dyspnea), level of consciousness (classified into 3 categories: normal, altered consciousness and coma according to the Pediatric Glasgow coma scoring system), and different triggers conditions. Anthropometric measurements (weight, height, body mass index, BMI (kg/m2) also expressed in standard deviation (BMI-DS), stage of pubertal development according to Tanner.
The severity of DKA was determined by the pH and concentration of plasma bicarbonates and was categorized into 3 groups: (a) mild: pH <7.30 and/or serial bicarbonate <15 mmol /L; (b) moderate: pH <7.2 and /or bicarbonate <10 mmol /L and (c) severe: pH <7.1 and /or bicarbonate <5 mmol/L (Table 1). According to ISPAD, new-onset T1DM with pH > 7.3 and HCO3 > 15 mEq/L was classified as T1DM without ketoacidosis.

**Ethics approval and consent of participate**: Informed written consensus was obtained from all patients' parents. It is approved by the Albanian National Ethics Committee.

***Statistical analysis***
Absolute numbers and corresponding percentages were used to describe the categorical data. To describe numerical data, the reporting of the central tendency measures, in this case the mean value, and the dispersion measures, in this case the standard deviation, was used.
The square hi test was used to compare categorical variables; in case the resulting table was in the size of 2x2, then the value of P was reported according to Fisher's exact test, which gives a more accurate calculation of the P-value.
To compare the mean values of the numerical dependent variable according to the categories of the independent variable, the non-parametric Mann-Whitney U test was used for two independent samples in the case where the independent variable had only two categories; otherwise, when the independent variable had >2 categories the non-parametric Kruskal Wallis test was used for k

independent samples. Non-parametric tests were used in case the dependent variable was found to be abnormally distributed in the study population. Otherwise, for normally distribute numerical variables, the student's t-test for two independent samples was used.
Binary Logistic Regression test was used to identify the associations between the presence of diabetic ketoacidosis and the independent variables. Various tables depending on the information were used to present the data. Graphs of different types were used to present and illustrate the study findings. In all cases, the associations between the variables were considered significant if the value of the statistical significance was ≤ 0.05 (or ≤ 5%). All statistical analyzes were performed through the Statistical Package for Social Sciences, version 26 (IBM SPSS Statistics for Windows, version 26) software program.

**Results**

A total of 152 (52% male and 48% female) children age < 15 years were diagnosed with type 1 diabetes mellitus (T1DM) during the study period. The mean age at diagnosis, age, sex and residence distribution of the study population are shown in Table 1. The mean age of the subjects at the time of diagnosis is 8.3 years ± 3.6 years. At the time of diagnosis, 40.1% were between ages 5-9 years, followed by 39.5% between ages 10-14 years and 20.4% younger than 5 years. Three quarters (75%) of children with T1DM live in urban areas and 25% in rural areas.

**Table 1. Mean age at diagnosis, age, sex and residence distribution of the study population**

| Variable | Frequency (%) |
|---|---|
| Mean age at diagnosis (Mean value ± standard deviation) | 8.3 ± 3.6 |
| **Age- Group** | |
| 0-4 years | 31 (20.4%) |
| 5-9 years | 61 (40.1%) |
| 10-14 years | 60 (39.5%) |
| **Gender** | |
| Male | 79 (52%) |
| Female | 73(48%) |
| **Residence** | |
| Urban | 114 (75%) |
| Rural | 38 (25%) |
| **Total** | 152 (100.0) |

Mean duration of symptoms to the diagnosis of T1D was 23.35 ± 17.16 days. No statistically significant gender differences were observed regarding mean duration of symptoms, while the age differences were statistically significant: 17.48 days among children 0-4 years old, 28.61 days among children 5-9 years old and 21.03 days among children 10 -14 years (Table 2).

**Table 2. Duration of symptoms to the diagnosis of T1DM**

| Statistical parameter | Time of onset of symptoms to diagnosis of DMT1 (in days) | P-value according to gender | P-value according to subgroups |
|---|---|---|---|
| Mean Average value | 23.35 | 0.362* | **0.013**** |
| The standard deviation | 17.16 | | |
| Median | 21.00 | | |
| Mode | 30 | | |
| Minimum value | 0 | | |
| Maximum value | 90 | | |
| The spectrum | 90 | | |

* P value according to the non-parametric Mann-Whitney U test for two independent samples.
** P value according to the non-parametric Kruskal Wallis test for k independent samples.

At diagnosis of T1D1, 13.8% were misdiagnosed as viral infection, gastrointestinal and respiratory airways infection and less often as surgery emergency.

**Table 3. Misdiagnosis at new onset of T1DM**

| Variable | Frequency (%) |
|---|---|
| **Suspicion of diabetes at the time of admission** | |
| No | 21 (13.8%) |
| Yes | 131 (86.2%) |

Family history for DMT1 were in 15.8%, DMT2 in 17.8% and both types in 2.6% of the children. Among children with a positive family history of DMT1, the grandfather/grandmother was most often affected (54.2%), followed in 29.2% of cases by the brother/sister.

**Table 4. Family history and T1DM and/or T2DM**

| Variable | Frequency (%) |
|---|---|
| **Family history with T1DM** | 24 **(15.8%)** |
| **Family history with DMT2** | 27 **(17.8%)** |

**Figure 1a. Positive family history of T1DM**

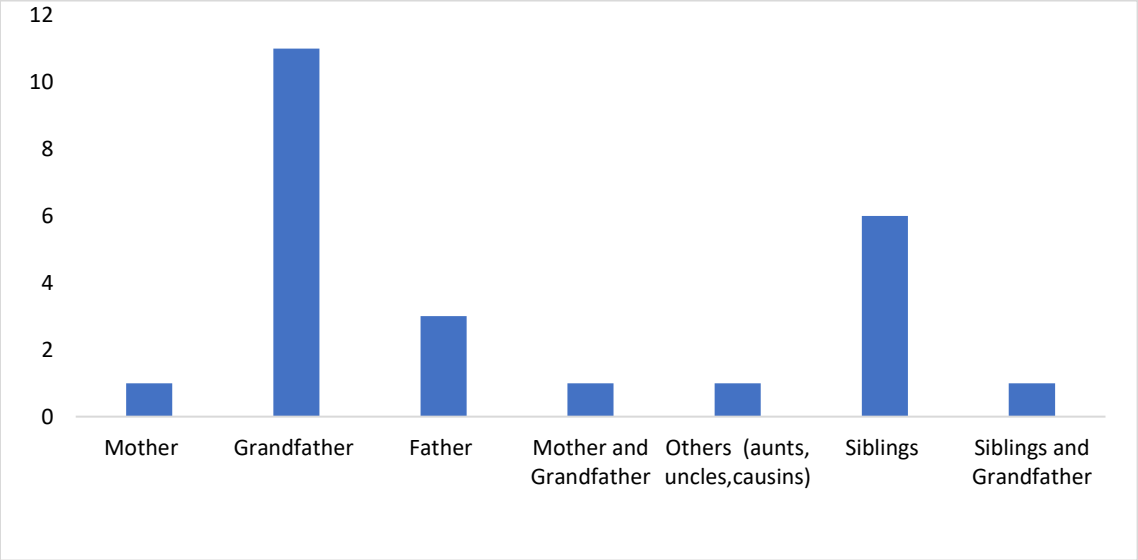
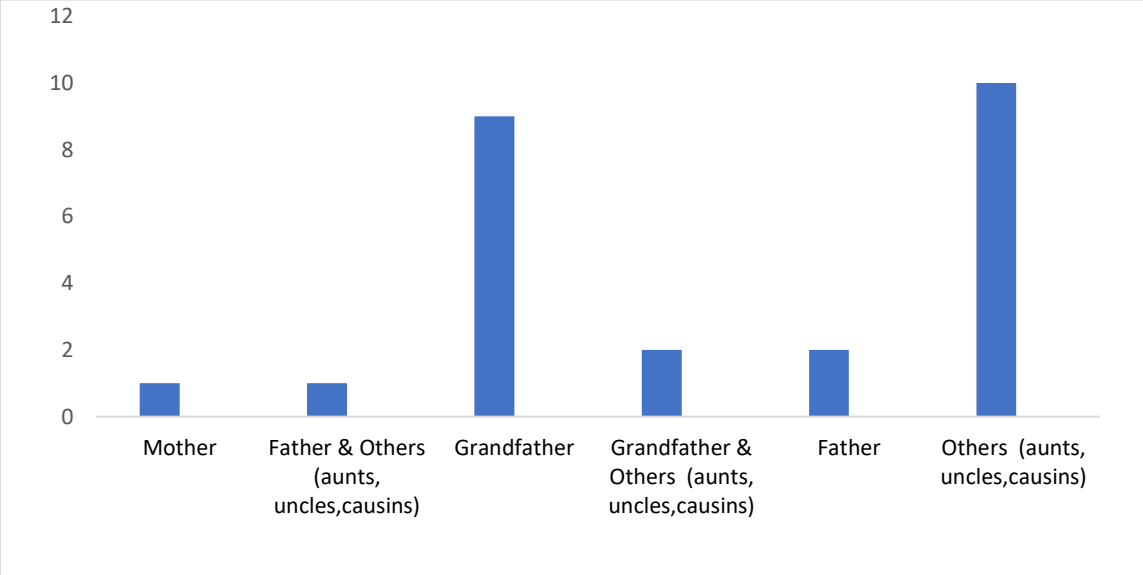



**Figure 1b. Positive family history of T2DM**

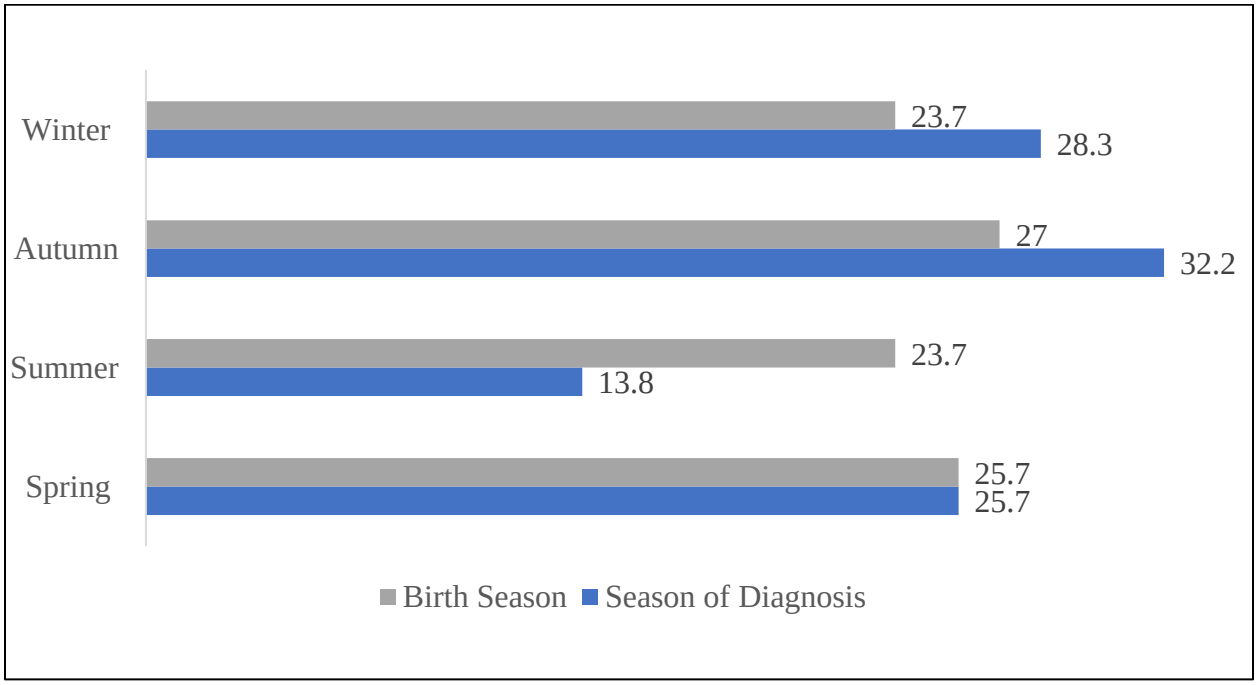



Regarding the season of birth and the season of diagnosis of type 1 diabetes of the children in the study, it is noted that approximately 1/4 of the children were born in each of the seasons of the year. However, more than half of DMT1 were diagnosed in autumn and winter (60.5%).

**Table 5. Distribution of children at diagnosis of T1DM according to the seasons of birth and seasons of diagnosis**

| Birth Season | 0-4 years | 5-9 years | 10-14 years |
|---|---|---|---|
| Spring | 8 | 14 | 17 |
| Summer | 6 | 15 | 15 |
| Autumn | 7 | 21 | 13 |
| Winter | 10 | 12 | 14 |
| **Total** | 31 | 62 | 59 |
| **Season's Diagnosis** | | | |
| Spring | 3 | 18 | 18 |
| Summer | 5 | 8 | 8 |
| Autumn | 13 | 20 | 16 |
| Winter | 10 | 16 | 17 |
| **Total** | 31 | 62 | 59 |

**Figure 2. Distribution of diagnosis and frequency of birth in different seasons of year**




The data analysis showed that most of the children were born in the spring−summer months (53.23%) compared to the autumn−winter months (46.77%) (Figure 3a). Most of the children were born in December, followed by those born in November, April, august and September (Figure 3a). Significantly more children were diagnosed with T1DM during the colder months of the year, October−March (53.3%) compared to 46.7% during the warmer months, April−September (Figure 3b).

**Figure 3. a) Distribution of children according to month of birth.**
**b) Frequency of diagnosis of T1DM during the cold and warm months**

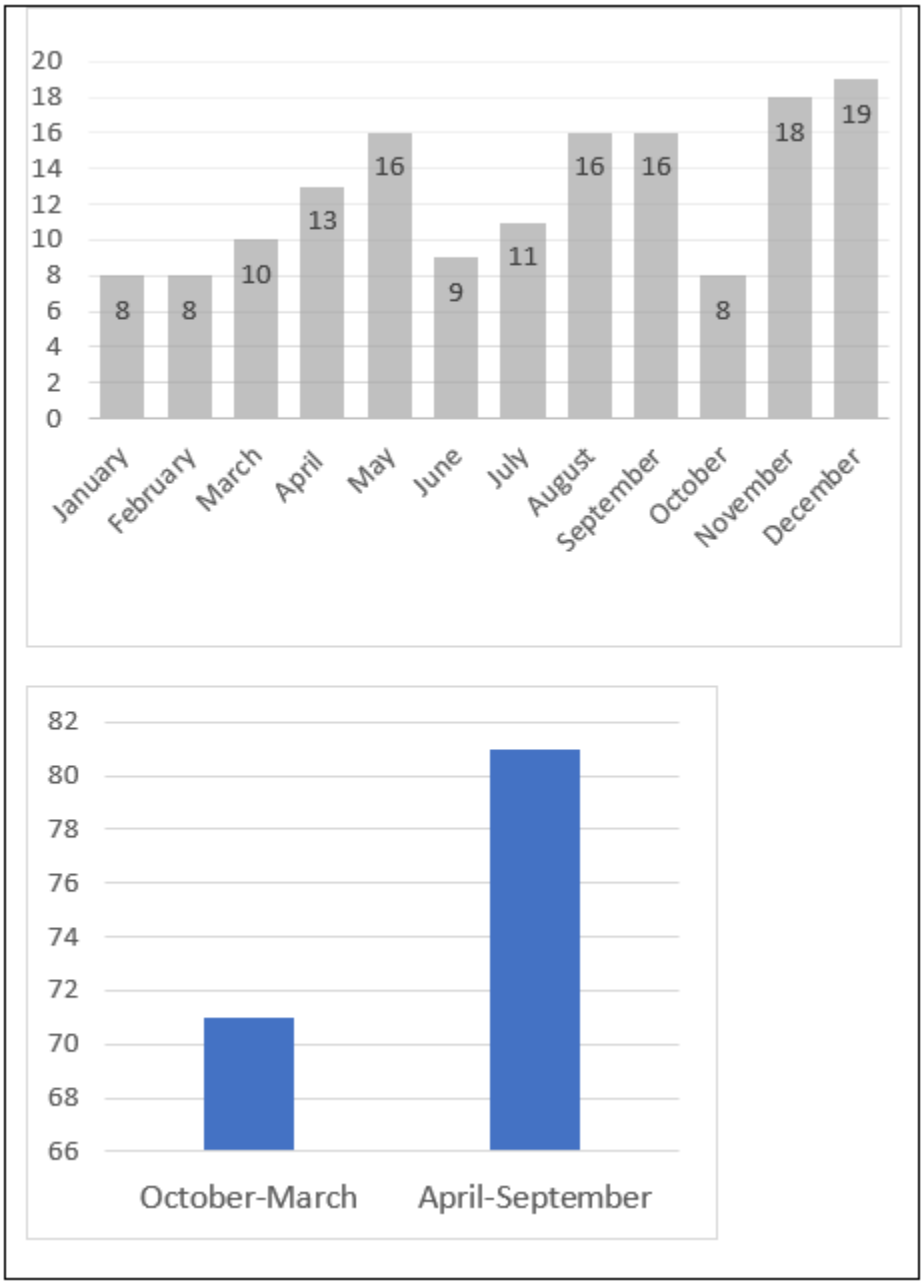
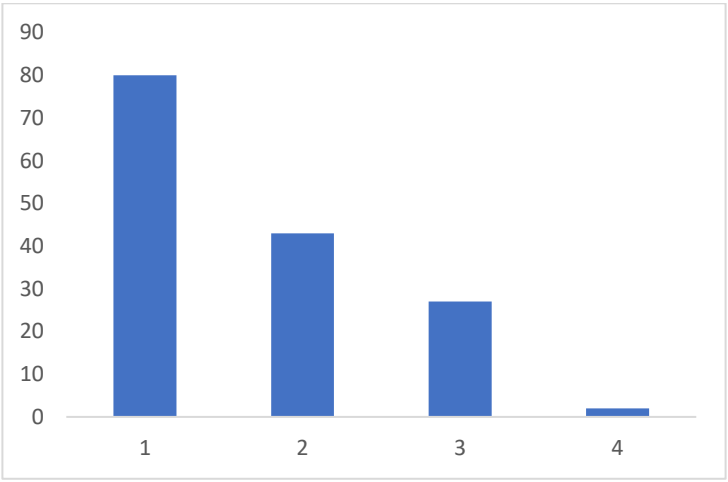


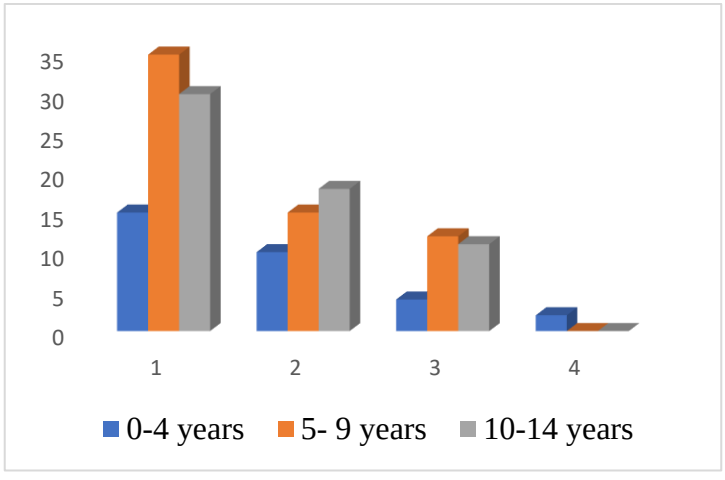
**Table 6. Birth order**

| Birth order | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Total | 80 | 43 | 27 | 2 |
| 0-4 years | 15 | 10 | 4 | 2 |
| 5-9 years | 35 | 15 | 12 | 0 |
| 14-10 years | 30 | 18 | 11 | 0 |

52.63% of the patients studied were first born, 28.3% were the second child of the family, 17.8% were the third child, 4.6% the fourth child and 1.3% were the fifth child (Fig. ). The differences observed with respect to the order of birth are statistically significant (chi-squared test, $p < 0.001$).

**Figure 4. a) Birth order**
**b) Birth order according to the age**



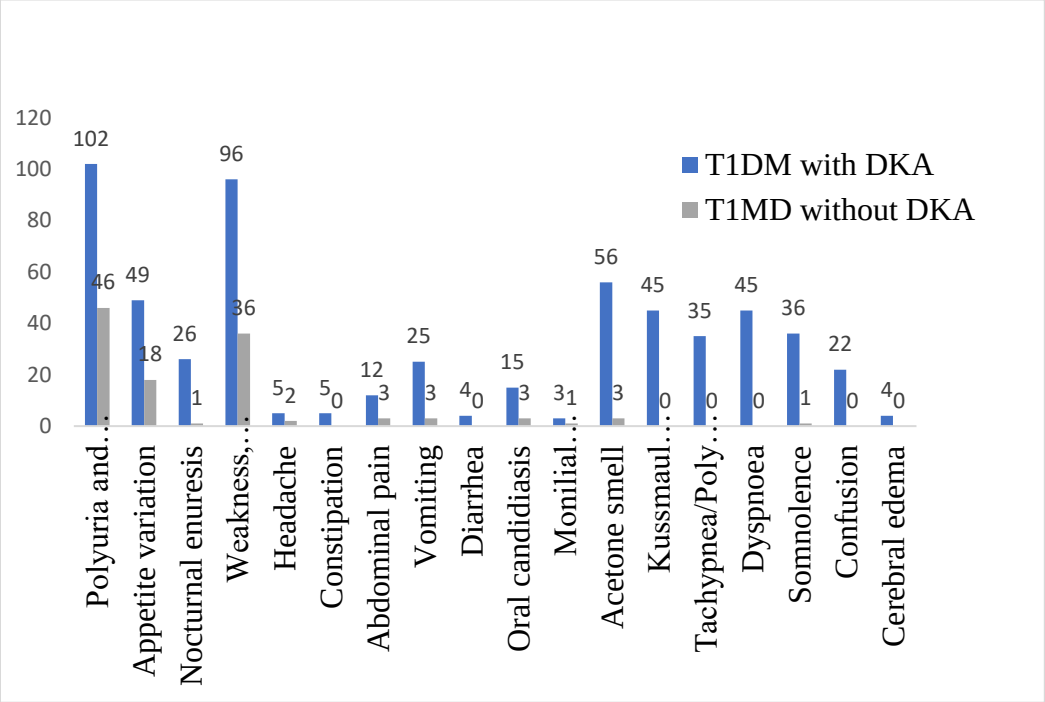

The mean birth weight of our study group was $3325 \pm 463.8$ g (min: 1500 g, max: 5100 g). 1.3% of the patients had a birth weight below 2500 g, 70.4% between 2500

and 3500 g and 28.3% >3500 g. Most of the patients (82%) were born by normal vaginal delivery and 18% by cesarean section.

Among the children diagnosed with DMT1, in 23.7% of cases the presence of viral infections (enteroviruses, hepatitis, frequent upper respiratory tract infections, gastroenteritis) and one case chest trauma were identified. Psychosocial stress (divorce, death of a parent and family member) was observed in 2.6% of children. There were no statistically significant gender differences related to these indicators.

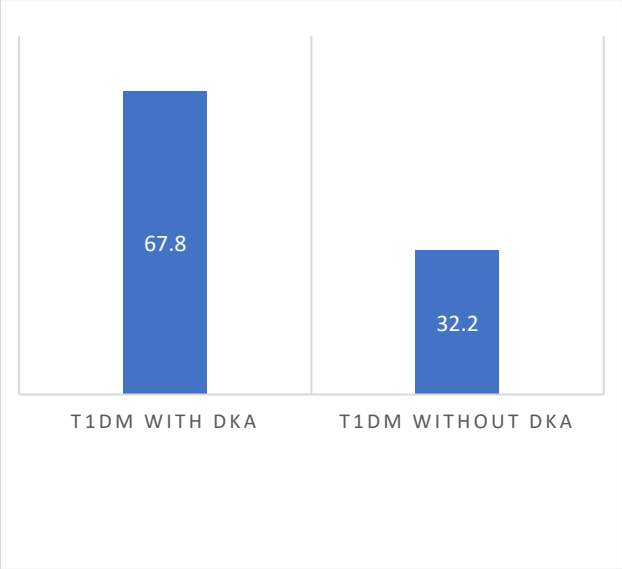
The percentage of viral infections history or other trigger conditions were higher in children aged 0-4 years (41.9%) compared to children aged 5-9 years (27.9) and aged 10-14 years (10%) [P=0.002] and no statistically significant age differences were observed regarding the psychosocial stress. Polyuria (100%), polydipsia (100%), and weight loss (98.1%) were the most common complaints. The frequency of malaise, vomiting, enuresis nocturnal, acetone odor, dyspnea, drowsiness and confusion was higher among children with DKA ($p < 0.001$).

**Figure 5. The presenting clinical manifestations of children and adolescents**




At the time of diagnosis, the overall incidence of ketoacidosis was 67.8%. The mean age of children with DKA was 7.75 ± 3.64 years, and 9.29 ± 3.39 years in children without DKA ($P = 0.012$). There were no statistically significant differences by age subgroup and living residence; the percentage of females was higher in T1DM children with DKA (54.4%) than among those without DKA (34.7%) ($p = 0.025$).

**Figure 6. Frequency of DKA at Diagnosis of T1DM**




Positive family history of type 1 diabetes increases the **Odds ratio (OR)** of the presence of DKA by 1.52 times, and positive family history of type 2 diabetes decrease 1.56 (1/0.64) times the presence of DKA (protective role), compared to children without family history for DMT2 but this difference is not statistically significant (P>0.05). A positive family history for both DMT1 and DMT2 increases the likelihood of the presence of KAD by 8.73 times, but even these differences did not reach statistical significance (P>0.05).

Viral infections and other trigger conditions increase the likelihood of the presence of KAD by about 1.58 times; however, there were not statistical significance difference (P> 0.05).

Regarding the association of psycho-social stress and presence of KAD in type 1 diabetes, seems that psycho-social stress may be a risk factor for the presence of DKA in diabetic children (being that 3.9% of diabetic children).

**Table 7. Association between the presence of DKA in diabetic children and selected variables – Odds ratio (OR) by Binary Logistic Regression test**

| Variable | OR § | 95% CI * | | P-value † |
|---|---|---|---|---|
| | | Lower Interval | Upper Interval | |
| Positive family history of T1DM | 1.52 | 0.56 | 4.10 | 0.411 |
| Positive family history of T2DM | 0.64 | 0.27 | 1.50 | 0.300 |
| Positive family history of T1DM or T2DM | 6.00 | 0.60 | 59.80 | 0.127 |
| Positive family history of T1DM and T2DM | 8.73 | 0.82 | 92.85 | 0.073 |
| Viral infections and other trigger conditions | 1.58 | 0.68 | 3.68 | 0.290 |

| | | | | |
|---|---|---|---|---|
| Female with DKA | 2.24 | 1.11 | 4.54 | 0.025 |
| Subgroup 0-4 years with KAD | 2.97 | 1.06 | 8.32 | 0.038 |
| Age (year) | -0.126 †† | | | 0.016 |
| Urban residence and DKA | 1.32 | 0.61 | 2.84 | 0.484 |
| Duration of signs and symptoms (day) | 0.015 †† | | | 0.179 |

§ Odds ratio (OR) of the presence of KAD in diabetic children versus its absence, according to the Binary Logistic Regression procedure;
* 95% confidence interval (95% CI) for OR;
† Statistical significance value (P value) according to the Binary Logistic Regression test.

Table 8 presents the association of the KAD with symptoms and signs of children in the study. It appears that presence of nocturnal enuresis, malaise, vomiting, acetone smell and drowsiness increase the odds of the presence of DKA in diabetic children by 16.21, 4.95, 4.98, 18.27 and 25.79 times, respectively, and these differences are statistically significant (P<0.05). It must be said that Kussmaul respiratory distress, polypnea/tachypnea, dyspnea, confusion and cerebral edema/coma appear to be significant predictive factors of the presence of DKA in diabetic children, but the absence of these signs in children without KAD made binary logistic regression analysis impossible.

**Table 8. Association between the presence of DKA in diabetic children and selected variables – Odds ratio (OR) by Binary Logistic Regression test**

| Variable | OR § | 95% CI * | | P-value † |
|---|---|---|---|---|
| | | Lower Interval | Upper Interval | |
| Nocturnal enuresis | 16.21 | 2.13 | 123.35 | **0.007** |
| Malaise | 4.95 | 1.83 | 13.40 | **0.002** |
| Headache | 1.20 | 0.22 | 6.41 | 0.832 |
| Abdominal pain | 2.02 | 0.54 | 7.52 | 0.294 |
| Vomiting | 4.98 | 1.42 | 17.41 | **0.012** |
| Oral candidiasis | 2.61 | 0.72 | 9.49 | 0.144 |
| Monilial vaginitis | 1.44 | 0.15 | 14.21 | 0.755 |
| Acetone smell | 18.27 | 5.34 | 62.54 | **<0.001** |
| Somnolence | 25.79 | 3.42 | 194.67 | **0.002** |
| Glycaemia | 0.006 †† | | | **0.001** |
| pH | -78.275 | | | 0.022 |
| HCO3 | -0.312 | | | 0.001 |
| Triglycerides | 0.009 | | | 0.009 |

Table 9 presents the relationship between the presence of DKA and some laboratory parameters of the diabetic children in the study. Data analysis showed that blood glucose and triglycerides are positively related to the presence of DKA, being that each additional unit of glycemia and triglycerides increases the odds of DKA by 0.006 and 0.099 times, respectively, and these changes are statistically significant (P<0.05). In the meantime, pH and HCO3 are negatively related to the presence of KAD:

thus, one additional unit of pH and HCO3 decreases the likelihood of DKA by 78.275 and 0.312 times, respectively and these differences are statistically significant (P<0.05).

**Table 9. Association between DKA and laboratory parameters**

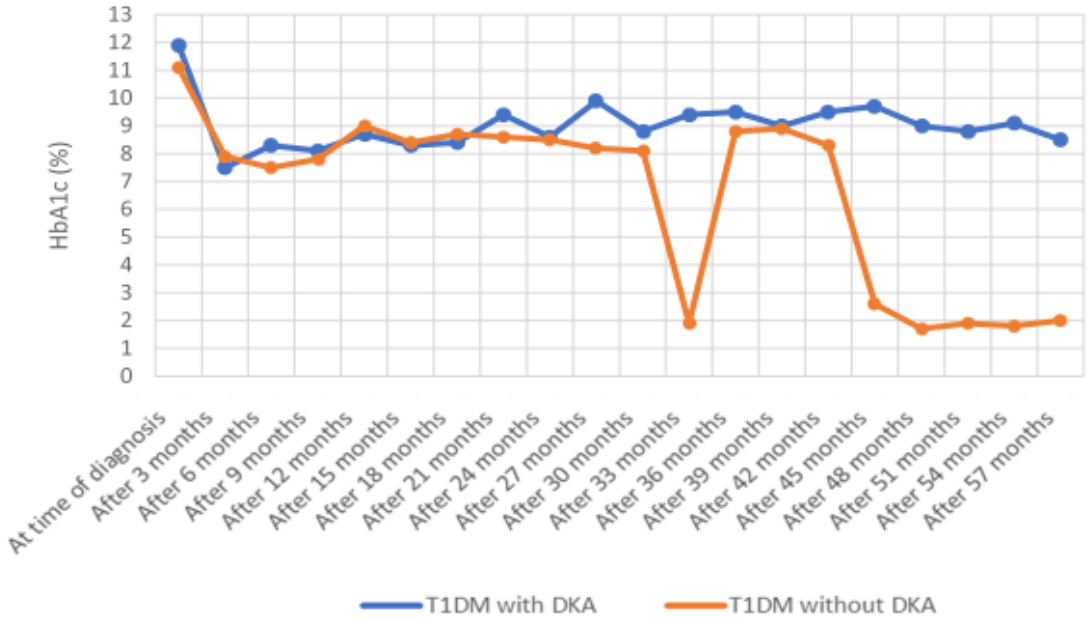
| | T1DM with DKA | T1DM without DKA | P-value |
|---|---|---|---|
| Frequency of DKA at diagnosis (%) | 67.8 | 32.2 | |
| Mean age | 7.75 ± 3.64 | 9.29 ± 3.39 | 0.012 † |
| Gender (male/female) (%) | 45.6/54.4 | 65.3/34.7 | 0.025** |
| Residence (urban/rural) (%) | 76.7/23.3 | 71.4/28.6 | 0.549** |
| Age-groups | | | |
| 0-4 years | 25 (24.3) * | 6 (12.2) | |
| 5-9 years | 43 (41.7) | 18 (36.7) | 0.082** |
| 10-14 years | 35 (34.0) | 25 (51.0) | |
| Duration of symptoms (days) | 24.65 ± 17.39 | 20.61 ± 16.51 | 0.169* |
| Family history of T1DM/T2DM (%) | 17.5/15.5 | 12.2/22.4 | 0.482/ 0.364** |
| Viral infections trigger | 26.2 | 18.4 | 0.316** |
| Serum glucose level (mg/dl) | 513.2 ± 193.2 | 386.5 ± 138.3 | <0.001 |
| Glycated hemoglobin (HbA1c) at baseline | 11.9 ± 2.0* | 11.1 ± 2.4 | 0.195 ** |
| Blood pH | 7.2 ±0.1 | 7.4 ± 0.1 | <0.001 |
| HCO3 | 8.7 ± 5.4 | 19.9 ± 4.5 | <0.001 |
| Triglycerides | 217.5 ± 189.9 | 118.2 ± 55.7 | 0.001 |
| Presentation with severe DKA based on venous pH (<7.1) | 17 (32.1) * | | <0.001** |
| Presentation with severe DKA based on HCO3 (<5) | 15 (28.8) | | <0.001** |

The mean HbA1c level of the total study population was 11.65±2.2%. HbA1c levels did not differ by age subgroups or gender.

| Age (years) | 0-4 | 5-9 | 10 -14 |
|---|---|---|---|
| Mean value HbA1c | 11.63 ± 2.05 | 11.76 ± 162 | 11.70 ± 1.76 |

There were no significant differences of mean HbA1c values between diabetic children with and without KAD (11.9 ± 2.0% *vs*. 11.1 ± 2.4%, p=0.195) at diagnosis and during follow up. The average values of HbA1c at diagnosis and over time in diabetic children with and without KAD are presented in the following Figure 7. It can be seen from the Figure 7 that the progress of HbA1c over time is more favorable for diabetic children without KAD compared to diabetic children with KAD, since in diabetic children without KAD the average level of HbA1c is constantly lower than in children with KAD, while in children with KAD the average level of this parameter remains more or less constant but at quite high levels (between 8-9%).

**Figure 7. Mean HbA1c level (in %) among diabetic children with and without DKA, during study**




* Mean value ± standard deviation.
** Statistical significance value according to the non-parametric Mann-Whitney test for two independent samples.

At diagnosis of T1DM, 17.10% (26/152) of the children had concomitant autoimmune diseases (AD): 14.47% (22/152) autoimmune thyroid disease (ATD) and 2.63% (4/152) CD; 65.38% (17/26) were female and 34.62% (9/26) male. Half of children (13/26) with autoimmune diseases were presented with DKA. According to the specific age group 7.7% were in the age group 0-4 years; 57.7% in the age group 5-9 years and 34.6% belong the group age 10-15 years old. At the time of diagnosis, among children with ATD, 68.2% were female, ages 8-10 were the most affected (59.09%), 23% children had TSH >5 mU/L and 77% of children were positive TPO and 80% e children with positive TPO had normal thyroid function. Among children that developed concomitant CD at diagnosis of T1DM, 2 patients were female and 2 males; 2 age group 0-4 years and 1 age group 5-10 years and 1 age group 10-14 years. Of these, 1 girl, age 1.4 years preceded the diagnosis of DMT1 by 4 months (table). During follow-up, 8.55% of children developed SAT and CD; 8 children CD and 4 children SAT. The mean age of developed of CD and SAT after the diagnosis of T1D were 2.19 and 2.54 years, respectively. Of these, 1 child developed SAT and CD; Hashimoto 1.023 years and CD 4.11 years after the diagnosis of dmt1.

**Table 10. Concomitant autoimmune diseases (AD) in children with T1DM**

| | Frequency (%) | AD at diagnosis of T1DM | | | AD post diagnosis of T1DM |
|---|---|---|---|---|---|
| Age (years) | | 0-4 | 5-9 | 10-14 | 12 /152 (7.89%) |
| ATD+CD | 26/152 (15.79%) | | | | 1 (0.66%) |
| Female | 17/26 (65.38%) | 1 (5.9%) | 10 (58.82%) | 6 (35.3%) | |
| Male | 9 /26 (34.62%) | 1 (11.11%) | 5 (55.56%) | 3 (33.3%) | |
| ATD | 22/152 (14.47%) | | | | 5 (3.96%) |
| Female | 15/22 (68.2%) | | | | 4 |
| Male | 7/22 (31.8%) | | | | 1 |
| CD | 4/152 (2.63%) | 2 | 1 | 1 | 8 (35%) |
| Female | 2 | | | | 4 |
| Male | 2 | | | | 4 |
| TSH > 5 mU/L | 6 (23%) | | | | |
| Ac. anti TPO > 25 IU/ml | 20 (77%) | | | | |
| DKA | 13 (50%) | | | | |
| Positive TPO & normal thyroid function | 16/20 (80%) | | | | |
| Mean age after diagnosis of T1DM | | | | | |
| SAT | | | | | 2.19 years |
| CD | | | | | 2.54 years |

**Discussion**

The study included 152 children and adolescents aged 0-14 years, diagnosed with DMT1, presented to the Pediatric Department, "Mother Teresa" University Hospital, Tirana during the period January 1, 2010 to on December 31, 2014. To our knowledge, there are no similar studies conducted earlier in Albania that illuminate the epidemiological characteristics of children with DMT1. In this context, the present study takes a greater importance.

DMT1 is one of the most common autoimmune chronic metabolic diseases in children and adolescents. The incidence of childhood onset type 1 diabetes is increasing by ~50% every 10 years (1,4).

According to the data of the International Diabetes Federation (IDF) 2017 (23), the number of children and adolescents living with diabetes during the last decades is growing rapidly, especially among younger children.

In European population the incidence of type 1 diabetes varied tenfold (24); from the lowest in Georgia (4.6/100,000/year) to very high in Finland (62.3/100,000/year) (25). However, most European countries have intermittent incidence (5.0-9.99 per 100,000 population) (1).

During the 2010-2014 study period, the incidence of T1DM among Albanian children ages < 15 years was 5.012/100,000/year, places Albania among countries with middle risk (1).

Countries that have an incidence of T1DM close to Albania are Belarus (5.6), Romania (5.4) and Macedonia (5.8) (25). Besides North Macedonia, Bosnia-Herzegovina (8.2) and Croatia (9.1) (25), other countries of the Southern European region, have a high incidence (10-19.99/100,000/year) (1).

In general, the incidence increases with age until middle puberty, with a peak at age 10–14 years compared to other ages is attributed the rapid hormonal changes (26,27) and decreases after puberty, particularly in females compared to young male adults (28,29). Approximately 45% of children are first presented before age 10 (30). The mean age of children with T1DM included in this study was 8.3 ± 3.6 years. In our study, at the time of diagnosis of DMT1 about 40% were 10-14 years old; 40% were 5-9 years old and 20% were 0-4 years old of children with diabetes. These findings are consistent with international literature data.

Interestingly, in SEARCH study the distribution of children with diabetes by age group was about 21% of children 0-4 years, in the Philadelphia registry, 37% were 5-9 years and 41% were 10-14 years (26), quite similar to that of our study. According to the EURODIAB registry, 24% of children with type 1 diabetes were 0–4 years old, 35% were 5–9 years old, and 41% were 10–14 years old (26), these results are quite similar to the findings of our study. A study in France of 1299 children 0–14 years old at the time of T1D diagnosis reported that 26% were 0–4 years old, 34% were 5–9 years old, and 40% were 10–14 years old (31**)**, these findings are completely similar to the age distribution of T1DM evidenced in our study.

Although most autoimmune diseases more commonly affect females, in the overall incidence of childhood T1DM there no gender difference. In our study, it was observed an almost equal gender distribution among children with type 1 diabetes; 52% male and 48% female. These data are also supported by international studies. The SEARCH Study on Diabetes in Youth reported both genders are equally affected by type 1 diabetes (26).

Type 1 diabetes mellitus is characterized by global, modest seasonal variation, with the highest incidence in the cold months (autumn-winter) and the lowest in the warm months (spring-summer). (32) The DiaMond Project demonstrated that the seasonality of the incidence of type 1 diabetes mellitus in children ages < 15 years is a real phenomenon. Statistical differences in the seasonality of the development of type 1 diabetes have been found in populations with intermediate and high incidence compared to the general population (3,33).

There is a significant tendency of younger patients to be diagnosed in the cold months. The reason for this seasonal difference is not completely understood, it may be related to the pathogenic role of various environmental triggers including infections encountered more frequently in the younger age groups, especially due to kindergarten enrollment, although there are no definitive conclusions regarding the role of specific infections in the occurrence of DMT1 (34). A study among children ages 0-14 years in Bulgaria reported that a greater proportion of children with DMT1 were diagnosed during the autumn-winter period (about 62.5%) (35), a figure completely similar to the finding in our study where 60.5% of children with DMT1 were diagnosed in autumn-winter.

In our study we did not observe any clear trend regarding the seasonality of the birth and diagnosis of children with DMT1, as about a quarter of children with DMT1 were born and about a quarter of them were diagnosed in each season of the year. However, 60.5% of DMT1 cases in our study were diagnosed in autumn-winter and 39.5% in spring-summer.

There is a connection between the month of birth and the development of DMT1 during the later stages of life (34). Children born during the spring and summer months, especially in countries with intermediate incidence such as Eastern European countries, have a higher risk of developing type 1 diabetes compared to children born during the fall and winter months (36,37). It

is thought to be related to seasonal environmental factors during fetal-perinatal life and thereafter (38) which influence fetuses and children to develop islet autoimmunity (6,23,39) and the disease at different ages (34). Our finding was similar to a study in Greece (40), while several other studies reported the opposite (26,34).

Seasonal character of birth month and T1DM development in some sub-populations is related to gender, ethnicity and race, and viral infections. In some countries males born in the spring and summer months are prone to develop T1DM while in others predominate females (41). In our study, 56% (42/75) of children born in the spring - summer months were boys.

In homogenous populations despite incidence of type 1 diabetes children born in the spring - summer months have a higher risk of developing type 1 diabetes, while this association is not in ethnically heterogeneous populations (42). The increased risk of T1DM manifestation in children born in spring-summer is also related to viral infections including enteroviruses, rotavirus, mumps virus, cytomegalovirus, rubella virus, etc. based on serological, immunological findings (43).

A variety of infections play a role in the conversion of endogenous beta-cell antigens into immunogenic structures, where infiltration of the islets of Langerhans, by activated autoreactive T cells is considered to be the major driver of the onset and progression of type 1 diabetes mellitus. If the pregnancy occurs during the months with the highest presence of viral infections (43) they are more likely to be infected and to transmit the virus to the fetus. Consequently, given a normal gestation period of 40 weeks, children born in spring and summer are more likely to develop type 1 diabetes.

The order of birth has been associated with T1DM presentation. The study by Eirini Kostopoulou., et al 2021 (44); Chris R Cardwell., et al. 2011 (45) showed increase the risk of childhood type 1 diabetes in first born children and reduction risk in second- or later born children particularly among children aged <5 years. The cause of any increase in the risk of childhood type 1 diabetes in first born children is unknown. It is possible related with younger maternal age, maternal prenatal immune response to environment exposures (46), congenital infections and use of antibiotics by mothers during pregnancy (43), reduced or delayed exposure to infections such as enteroviruses (47), household with older siblings who are exposed to infectious agents at school or day care or parents pay attention differently for their first child compared with subsequent children. Our findings are consistent with international literature data. This finding may provide indirect support for the hygiene hypothesis, which suggests that the immune system requires stimulation by infections and other immune contests in early life to achieve a mature and balanced repertoire of responses (48). The higher incidence of DMT1 in Western countries can be dedicated to the phenomenon of "hygiene hypothesis"; according to this hypothesis, decrease of the frequency of infections of diabetogenic viruses may lead to an increase in the incidence of DMT1 (43). However, exposure to viruses does not necessarily appear to be the cause of DMT1 but rather may be beneficial in some cases (43).

Regarding viral infections in our country, data is not available. A relatively low level of hygiene, especially in rural areas point toward that viruses are one of the main etiological factors of T1DM. Based on the fact that in our study only 25% of diabetic patients lived in rural areas, it appears that this study supports that part of the literature that emphasizes a protective role of viral infections in the development of DMT1 in children.

In our study, three quarters of children with T1DM lived in urban areas. Such finding has been evidenced into similar studies conducted in the Balkan countries (35). However, other studies have evidenced a higher incidence of DMT1 among children living in rural areas (49-53) suggested that the higher incidence of DMT1 in rural areas may be related to a lower exposure of these children to protective environmental factors (53).

The international literature suggests the role of psycho-social stress in the development of T1DM in children. A study among 338 children with DMT1 aged 0–14 years in Sweden and 528 controls suggested that stressful life events (threats or fear of losing family members, such as divorce or death of parents) adverse psychosocial stressful events (including events with difficult adjustment, child behavioural deviations, and disordered and chaotic family functioning) 12-24 months before the diagnosis of T1DM, during the two years before T1D diagnosis in children statistically significantly increased the risk of T1D (54) and may have different impacts at with a relative risk (RR) of 1.82 in different ages (55). The stressful life events, are associated with the development of T1D in children aged 5-9, acting as a risk factor for this disease (56). In our study, we did not have a comparison group to analyse whether stressful psychosocial life events are a risk factor for T1DM in children, but psychosocial stress related to parental divorce or death was evidenced in 2.6% of children with T1DM at aged 5–9 years compared to the children aged 0–4 and 10-14 years, confirming the findings of the study in Sweden. Further studies can be undertaken to verify whether psychosocial stress is a risk factor for T1DM in our country.

In our study, it was found that 23.7% of children with DMT1, had a history of precipitating viral infections, significantly higher among children aged 0-4 years (41.9%) compared to children aged 5-9 years (27.9) or those aged 10-14 years (10 %) [P=0.002].

More than 85% of individuals who develop type 1 diabetes have no family history, so the general population screening to identify risk in is an important goal (56).

In our study we found that 15.8% of children with DMT1 had a family history of DMT1, 17.8% had a family history of DMT2, 28.3% had a family history of DMT1 or DMT2, and 2.6% had a family history of both DMT1 and DMT. The genetic component of the development of DMT1 is known. The risk of developing DM1 in first degree relatives is 8 to 15 times higher (57-59) and about twice as high in second-degree relatives compared to children with no relatives with diabetes (57-60). About 10-12% of children with T1DM have a family history of diabetes at the time of diagnosis, which may increase more than 20% during their lifetime (60-63) data which are very similar to the findings of our study. A study among 1488 children aged 0–14 years in Finland reported that 21.8% of them had a first- or second-degree relative with type 1 diabetes at the time of diagnosis (64).

The fathers transmit DMT1 to their offspring more often than mothers (58,65). Similar findings were observed to our study: 12.5% of children with DMT1 had a father and only 8.4% of them had a mother with DMT1 at the time of diagnosis.

Different studies have reported different data regarding the time between the appearance of symptoms and the moment of diagnosis. The duration of symptoms to the diagnosis can vary greatly, ranging from a few days to several weeks or months depending on the level of education of the parents, the fact of the presence of diabetes in other family members, level of health care, the age of the patient, etc. (66). The average duration of symptoms to the diagnosis of DMT1 in our study we was 23.35 ± 17.16 days, ranging from 0 days (immediate diagnosis) to a

maximum of 90 days (ie, 3 month). Our results regarding the duration of symptoms were similar to those reported by Demir F, et al (67) and Usher-Smith et al (68). The age of the patient is important because younger patients usually present with mild, vague symptoms, while older children usually present with the classic symptoms of the disease such as polyuria, polydipsia and weight loss (66). Younger children are more likely to present in severe stages of the disease, reflecting this in a higher frequency of ketoacidosis (KAD) compared to older children due to higher levels of respiratory and gastrointestinal infections in this group, which may delay diagnosis (66). It has been proven that the diagnosis of DMT1 can be established later in girls than in boys, for unknown reasons (66). There are no statistically significant gender differences regarding this parameter, but there are significant age differences where this time was longer in children 5-9 years old (28.61 days) (p = 0.013).

Polyuria, polydipsia and weight loss were the most common symptoms, 99.3%, 99.3% and 98.1%, receptively. The second and most serious, life-threatening presentation of T1DM is DKA. Although the incidence of DKA in many developed countries has been reduced (69-71), various studies around the world reported a 6-fold variation of DKA in presentation from 12.8% to 80% of children diagnosed with T1D for the first time (72). In our study the overall incidence of ketoacidosis was 67.8%. The mean age of children with DKA was 7.75 ± 3.64 years, while that of children without DKA was 9.29 ± 3.39 years (P = 0.012). The mean age at diagnosis of children with DMT1 with KAD is significantly higher than that of children with DMT1 without KAD (24.65 ± 17.39 vs 20.61 ± 16.51, P=0.169). In general, children with DMT1 with KAD are diagnosed earlier than children with DMT1 without KAD, possibly because of their more gravity of clinic. In our study we found that the frequency of DKA was higher among girls (76.7%) than among boys (59.5%) and this difference was statistically significant (P = 0.025). The higher frequency of DKA among girls with T1D than among boys with T1D is also reported in the international literature. The girls were stated to experience DKA more frequently, possibly due to some sex-related social or biological differences (72). Our results were similar to the data of Demir F., et al (67).

Females and ages 0-4 years were identified as factors related to the presence of KAD in children with T1DM; 2.24 and 2.97 times, respectively more likely to be affected by KAD compared to males and children ages 10-14 years, respectively (P<0.05). Nevertheless, was evidenced a negative and statistically significant relationship between age and the presence of KAD: for every year increase of the age of children, the possibility of the presence of KAD decreases by 0.126 times.

Positive family history for dmt1 is considered a protective factor and is associated with a reduced risk of DKA at T1DM diagnosis because cases are diagnosed in an earlier stage (73). Our results did not reach agreement with these findings. Pawlowicz et al (74) and also reported that a positive family history had no such impact.

Positive family history for DMT1 and DMT2 was not statistically significantly associated with the presence of KAD in children with DMT1. However, children who have a positive family history of DMT1 or DMT2 were 6 times more likely to be affected by KAD (P=0.127); children with a history of DMT1 and DMT2 were 8.73 times more likely to be affected by KAD compared to children with DMT1 without a positive family history of DMT1 or DMT2 (P=0.073, borderline). The presence of viral infections or other precipitating conditions increased the odds of KAD by 1.58 times compared to

children without these conditions, this difference did not reach statistical significance. Regarding residence, children living in urban areas are 1.32 times more likely to be affected by KAD compared to children in rural areas.

The misdiagnosed were in 13.8% of cases, of which respiratory and gastrointestinal and infectious illnesses were the most common. Almost all were presented with KAD; and almost half (45.3%) were in the age group 0-4 years Similar results were found in the study Małgorzata Pawłowicz et al (14.13%) (74).

Autoimmune diseases are more common in females. In children and adolescents with T1DM of both genders carry similar risk and have no significant differences in overall incidence (75). The gender predominance of DMT1 is thought to be influenced by race, age of diabetes diagnosis, and incidence. In certain populations the incidence of DMT1 is more frequent in males (76) and in some more frequent in females (77).

In Caucasians, in high-incidence countries (23/100,000/year) (78), children ages < 6 and ≥13 years of European origin (age group which is more likely to develop diabetes for the same age and geographical localization (male: female ratio 3:2) (79) men have a slightly higher incidence than females. On the other hand, the female predominance is seen in of non-Caucasian origin (80), African and Asian, low incidence countries (81), peripubertal age (82).

Age, urban residence and year of diagnosis (35) and factors are related to viruses' infections, dietary factors such as gluten, obesity in childhood, improvement of hygienic-sanitary conditions, etc. (83) are statistically significant risk factors for the occurrence of DMT1 in children.

T1DM is associated with an increased risk of developing other autoimmune diseases as a result of genetic susceptibility to autoimmune diseases (AD). The most common comorbidities include: autoimmune thyroid disease (ATD) and celiac disease (CD) (84), possibly because of some common pathogenetic mechanisms including certain gene expressions (34). These AD are observed more frequently in females with T1DM (85).

At diagnosis and during follow up of T1DM 19.74% (30/152) developed associated autoimmune diseases; 11.85% ATD and 7.89% CD. Of them, 60% at diagnosis of T1DM and 68% of patients were female. During follow up children with T1DM developed associated CD and SAT, 2.54, and 2.19 years, respectively. These findings are consistent with international literature data.

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