ABSTRACT

Type 1 diabetes mellitus (T1DM), a chronic disease resulting in insulin deficiency due to beta cell destrucion, is becoming a frequent disorder in children. The prevalence of T1DM is increasing globally and varies between countries. There are various etiological factors including genetic, environmental and infectious. T1DM can lead to acute and long-term complications.

Diabetic ketoacidosis (DKA) is a life threatening condition often occuring at the onset of T1DM. In Poland, the prevalence of DKA is 22-30% at the onset of T1DM. The management of DKA requires hospitalisation, intravenous fluid and insulin treatment and can lead to complications. In the majority of patients, after the initial treatment, clinical partial remission period with decreasing insulin requirement is observed. In european countries incuding Poland, the incidence of T1DM is increasing, especially in children younger than 5 years old. The spreading of T1DM should increase the accurate identification of early symptoms as well as fast diagnostic pathways and proper treatment within general practitioners and pediatricians.

To date, there is not enough research assesing and analyzing variability of biochemical and clinical parameters in patients with the new onset of T1DM as well as analyzing the guidelines of treatments over the course of years.

AIM: The aim of the study was to analyze data of patiens with new onset of T1DM including demographic and biochemical parameters as well as clinical presentation. In addition, the comparison between specific guidelines and given treatment was drawn.

The following variables were analyzed:

– fluctuations within demographic, biochemical and clinical parameters in patients with the new onset of T1DM throughout the years

– pharmacological treatment in patients with T1DM

– comparison between specific guidelines and given treatment

– assessment of long-term treatment in patients with T1DM – indentifying factors affecting time of partial clinical remission, daily insulin requirement and metabolic control in comparison with initial demographic, biochemical and clinical parameters in patients with new onset of T1DM

Patients: The study was performed in Provincial Specialist Children's Hospital in Olsztyn between 01.01.2000 and 31.12.2018. 687 patients, aged between 0 and 18 years old, with a new

onset of T1DM, were enrolled in the study. 599 patients were administered intravenous insulin infusion. Comparative analyses were performed in several age groups (0-5, 6-10, 11-14, 15-18 years old) and time periods (2000-2002; 2003-2005; 2006-2008; 2009-2011; 2012-2014; 2015-1018).

Methods: Medical history data of patients with new onset of T1DM, hospitalized between 2000 and 2018 was collected. Demographic and biochemical parameters as well as the clinical presentation and treatment were analyzed. In addition, data including the time of partial cinical remission, the daily requirment of insulin and the metabolic control were collected from the Outpatient Clinic.

Statistical analisys: Microsoft Excell spreadsheets were used for data storage and processing. Statistical analysis was performed using STATISTICA 13PL sofware. Quantitative variables were expressed as the number of cases (N), mean (M), confidence interval ±95%, median (Me), minimum (Min), maximum (Max), the first and third quartile (Q, Q3) and standart deviation (SD). Qualitative (categorical) variables were expressed by comparing the number of cases (N) and their percentage ratio (%) within the study group. The distribution of results for independent variables was illustrated by the chi-square test (c2). The mean values of different groups were compared using student's t-test for direct comparison of two groups and ANOVA (F) for comparing a larger number of groups. Statistically significant results were found at the level of $p<0,05$. The significance of the difference in variables between groups was analysed with the ANOVA test of variance (F) for parametric distributions and the Mann-Whitney U test (U) for non-parametric distributions. Further analysis was performed with the post-hoc NIT test. Statistically significant results were found at the level of $p<0,05$.

Results: Demographic analysis- mean age of patients at the time of diagnosis of T1DM was 9,7 ± 4,4 years old, with girls being slightly younger. The study has shown a statistical decrease of the age of onset of T1DM since 2009. In the study group there were more girls.

The majority of patients – 63,03% were living in the city. In 62,2% of patients there were cases of diabetes within the family. The majority of children were born from the first pregnancy, full term with normal weight. Mean exclusive breastfeeding duration was 36,99 weeks.

The majority of patients were diagnosed with T1DM during winter season. The BMI in obese and overweight children has significantly increased during the years of observation – from 20,71 kg/m2 to 25,59 kg/m2 – while showing consistent values within the 3-year-period subsets.

Clinical presentation at the onset of T1DM- the majority of patients were admitted to the hospital in good to moderate state (severe in 12,66%). During the study, a tendency to admit new onset of T1DM in a good general condition was observed, in 3-year-period subsets. The average time of preceeding symptoms was 22 ± 20,3 days (median 14 days) and has been decresing within the 3-years-periods subsets of observation, while being significantly longer in girls and shorter in youngest children. The most common symtoms were: polyuria (94,32%), polydipsia (94,03%), nycturia (92,43%) and weight loss (88,21%). The most frequent associated diseas was fungal infection of the mucosa (67,54%). Hasimoto thyroiditis was the most common aoutoimmune disease in children with T1DM (16,3%).

Laboratory results at the admision: mean blood glucose was 453,65 ± 198,7 mg/dl, with a median of 410 mg/dl, mean pH was 7,32 ± 0,1 with a median of 7,36, mean base deficiency value was 8,58 ± 8,6, with a median of 5,7; mean HCO3 was 17,6 ± 6,9 mmol/l, with a median of 19,4 mmol/l.

Mean pH values (7,29 ± 0,14) in children between 0 and 5 years old were significally lower than in older children. DKA occured in 26,78% of patients. Children with DKA were significantly younger than children without DKA at the onset of T1DM. Severe DKA occured significantly more frequently in girls (15,96% vs 3,3%). In the study, the mean HbA1c was 11,73 ± 2,37%, with a median of 11,6%, being higher in girls and lower in younger children. During the study, HbA1c at the onset of T1DM was decreasing in 3-year-period subsets. Diabetic ketoacidosis complications: cerebral oedema in 0,58%, hypokaliemia in 21%, respiratory or gastrointestinal tract infections in 12,5%, behavioral problems in 3,2% of children, there were no cases of death within the study group.

Management of diabetic ketoacidosis: mean intravenous insulin treatment in the first day of treatment was 25,3 ± 11,4 hours (the longest in young children with a decreasing tendency) with mean dosage of 0,08 unit/kg/h (0,04 unit/kg/h within the first hour of treatement, 0,05 unit/ kg/h within the second hour). The 19 years of observation, showed a tendency to decrease the dosage of insulin, both interavenously and subcutanously, within 2-3 days of treatment and at discharge from the hospital. The doses of insulin were up to date with Polish Diabetes Association (Polskie Towarzystwo Diabetologiczne, PTD) guidelines.

Mean time: of intravenou fluid theraphy within the first day of treatment was 23,8 ± 11,5 hours, shorter in boys, longer in children with severe DKA. Mean amount of fluids was 4,11 ± 1,54 ml/kg/h, 7,65 ml/kg/h within the first hour, 6,76 ml/kg/h within the second hour of treatment,

leading to avarage decrese in blood glucose of 68,38 and 71,01 mg/dl within the first two hours of treatment. The administration of bicarbonate was rare, only necessary in 3,64% of patients during the first years of observation; it was not longer in use starting from 2015. Treatment including the use of fluids and bicarbonate was up to date with PTD guidelines.

Outpatients management: The mean time of care at the Outpatient Clinic was 74,79 months (6,24 years) ± 39,59, with a median of 72 month (5 years). Daily insulin requirement and HbA1c were anayzed at 3 months, 1 year after the diagnosis as well as throughout the whole observation as mean values within the whole study group. Mean daily insulin requirement 3 months after the diagnosis was 0,36 ± 0,22 units/kg and after 1 year of diagnosis – 0,48 ± 0,20 units/kg. Both values were similar within 3-year-period subsets - there were no statistical differences during the 19 years of observation.

In the study, mean value of HbA1c was 6,81% 3 months after the onset, and 7,27±1,11 % 1 year after the onset. There was a statistical decrease in the value of HbA1c in both time points within 3-year-perios subsets. In all the children during the 19 years of observation, the mean HbA1c was 7,88 ± 1,22%. There were no links between severity of DKA at the onset of T1DM and long-term metabolic control (HbA1c).

Mean HbA1c has significantly decreased within 3-year-period subsets: from 8,54 ± 1,23% (2000-2002) to 7,06 ± 1,02% (2015-2018). Mean daily insulin requirment was 0,77 ± 0,22 units/kg. There was a stasistically significant correlation between daily insulin requirement and duration of T1DM - the earlier the onset of T1DM, the larger the daily insuin requirment: 0,83 ± 0,23 units/kg between 2000 and 2002 and 0,68 ± 0,2 units/kg between 2015 and 2018.

Within the 19 years of observation, the prevalence of insulin pump use as a initial treatment was increasing, being compliant with the PTD guidelines.

Results:

1. The age of the children with new onset of T1DM significantly decreased throughout the years of observation.

2. Nourishment in patients with new onset of T1DM was similar throughout the years of observation. Even though, there were no significant changes within BMI in the study group, which does not confirm acceleration theory, in overweight/obese children there was an increase in BMI.

3. There were more patients with positive family history of diabetes, including T1DM.

4. There were no changes within accidental or delayed diagnosis as well as diagnostic errors in patients with new onset of T1DM throughout the years of observation. There was no improvement regarding knowledge of symptoms of T1DM, initial diagnosis, or misdiagnosing and treating accompanying T1DM infections.

5. The prevalence of ketoacidosis in patients with new onset of T1DM was stable at 30% throughout the years of observation. Diabetic ketoacidosis at the diagnosis of T1DM was significantly more frequent in younger patients.

6. Levels of HbA1C at the onset of T1DM have been decreasing within 3-year-period subsets suggesting a decrease of severity of hyperglycemia prior to diagnosis.

7. There were rare complications of diabetic ketoacidosis. There was no case of cerebral oedema during the 10 years of observation.

8. Insulin dosing has been decresing, both intravenously within first day of diabetic ketoacidos and subcutaneusly within 3-4 days of treatment. Bicarbonate (NaHCO3) was rarely used in the treatment of ketoacidosis. It is up to date with the applicable guidelines.

9. The prevalence of associated autoimmune disorders in children at the onset of T1DM is incresing. The most frequently encountered are autoimmune thyroid and celiac disease.

10. In recent years, the prevalence of partial clinical remission has been increasing. Remission

rates were the hightest in children between 6 and 10 years old. Remission was more common in children without acid-base disturbances or mild to moderate diabetic ketoacidosis at the onset of T1DM. The longest durations of clinical remission were observed in older children.

11. During the 19 years of observation, the average levels of HbA1C after the first year of T1DM were decreasing from 7,77% ± 1,26% during the first 3-year-period subset to 6,83%± 0,91% within the last

12. In the last years of observation, the common use of continuos subcutaneus insulin infusion was the most important factor increasing the prevalence of partial clinical remission as well as better metabolic control. In 2000-2002, only 4,17% of chidren with the new onset of T1DM, in contrast to 63,46% of patients between 2015-2018, were treated with insulin pumps at discharge from the hospital.