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Major variations in blood glucose levels in pediatric patients with type 1 diabetes

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ABSTRACT

Type 1 diabetes is one of the most common chronic diseases in children and adolescents, with an increasing incidence globally. Major variations in serum glucose cause severe ketoacidosis and hypoglycemia, acute metabolic complications of the disease. We performed a retrospective study on a group of 119 children and adolescents with type 1 diabetes in whom only the cases with ketoacidosis and severe hypoglycemia that required emergency hospitalization were quantified. At the same time, we identified the causes and determinants of these acute complications. According to the case study, 28.6% of patients (34 cases) presented severe hypoglycemia, the most common causes of hypoglycemia being intense physical activity without additional carbohydrate intake, delayed carbohydrate intake, and excess insulin. 15.3% of patients (18 cases) had ketoacidosis, of which 55.55% were recurrent ketoacidosis. Ketoacidosis has been detected in patients with poor glycemic balance and poor treatment compliance by not following a diet and skipping insulin doses. Among the additional risk fac-tors, we identified age over 13 years and the age of diabetes greater than 5 years, for both acute complications.

Keywords: type 1 diabetes, child, ketoacidosis, severe hypoglycemia

INTRODUCTİON

Type 1 diabetes is a chronic condition found in childhood and young adults, the pathogenic mechanism being autoimmune. In recent years, there has been a steady increase in the incidence of this disease (1,2). In addition to specific degenerative complications, the course of type 1 diabetes is exacerbated by acute metabolic complications, diabetic ketoacidosis, and severe hypoglycemia.

Data from the literature report that diabetic ketoacidosis, the most serious metabolic disorder, is identified in 15% to 67% of children and adolescents at the onset of the disease (3). Although it can be found in other types of diabetes, it is specific to patients with type 1 diabetes (4). Ketoacidosis is diagnosed at a glycemia >11 mmol/l (200 mg/dl), a venous pH < 7.3, bicarbonate < 15 mmol/l, with ketonuria and ketones in serum, biochemical criteria agreed by different international societies (ADA, ESPE) (5,6).

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Regarding the annual incidence of ketoacidosis, it is between 4.8% and 5.2% in children and young adults (7), while the mortality rate is 6% to 24% in developing countries and less than 1% in developed ones (8). The most severe complication of ketoacidosis is cerebral edema which can occur in about 0.5-1% of children, with a mortality rate of 20-25% (9).

With regard to diabetic ketoacidosis, apart from the physiological factors that condition the occurrence of ketoacidosis, there are also some additional risk factors. Small age (under 5 years), female gender, limited access to medical services, as well as unfavorable socio-economic status are discussed (10,11).

Regarding hypoglycemia, it is the main barrier to achieving very good glycemic control, severe hypoglycemia being the greatest fear of patients with diabetes and their parents (12). Depending on serum glucose levels, hypoglycemia may be mild (glycemia values between 54 and 70 mg/dl), moderate (glycemia less than 54 mg/dl) or severe (when another person's intervention is needed, with blood sugar usually less than 40 mg/dl) (13). Children who have already had a severe hypoglycemic episode in the last 12 months may be included in a risk group.

Among the neurological disorders associated with the acute phase of severe hypoglycemia, we mention transient mental deficit, electroencephalographic abnormalities, regional increase in cerebral blood flow. In patients with repeated severe hypoglycemia, especially in children under 5 years of age, permanent cognitive dysfunction may occur (14).

The paper aims to determine the prevalence of ketoacidosis and severe hypoglycemia in children and adolescents with type 1 diabetes, as well as to figure out the causes and factors favoring these complications.

MATERIALS AND METHODS

We present the results of a retrospective study conducted between January 2015 - December 2019 on a group of 119 children and adolescents with type 1 diabetes in the records of the Pediatric Diabetology office within the „St. Spiridon" County Emergency Clinical Hospital from Iasi. The data from the dispensary sheets and their treatment notebooks from the last 5 years were analyzed. The mandatory criteria for inclusion in the study were age under 19 years and the duration of disease evolution of at least 1 year. Only the cases with ketoacidosis and severe hypoglycemia that required emergency hospitalization were quantified, aiming to determine the etiology of these complications, as well as to establish correlations with certain parameters: age, gender, environment, age of the disease, insulin therapy regimen used, glycemic balance. The study was conducted according to provisions of the Helsinki Declaration (the local ethics committee approved the study) and all the patients signed the consent for the participation in this study.

SIGNIFICANCE ANALYSIS

All analyses were performed using SPSS. The ANOVA test, c^2 test, Kruskall-Wallis and "Pearson" correlation were used. All data are presented as the mean ± the standard error of the mean. $P<0.05$ was considered to indicate a statistically significant difference.

RESULTS

The analysis of socio-demographic characteristics showed a slightly higher frequency of male children (52.9%) and from rural areas (54.6%).

The current age of children varied between 3 years and 7 months and 18 years and 9 months, the average value being slightly higher in males (13.08 vs 12.74 years; p = 0.624) and in those from rural areas (13.33 vs. 12.42 years; p = 0.190) (Table 1).

The age of children at the onset of the disease ranged from 1 year and 7 months to 17 years and 4 months, with no significant differences in mean age between boys (boys 7.64 ± 3.71 vs. girls 7.84 ± 3.56 years; p = 0.769).

The age of diabetes varies between 1 and 14.7 years, registering an average value of approximately 5 years in both sexes (M 5.4 years vs F 4.9 years;

TABLE 1. *The average age of children mean age depending on gender and origin*

Characteristics	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min years	Max years
					Lower Bound	Upper Bound		
Sex								
Male	63	13.08	3.81	0.48	12.12	14.04	3.70	18.70
Female	56	12.74	3.80	0.51	11.72	13.75	4.10	18.90
Origin								
Urban	54	12.42	4.03	0.55	11.32	13.52	3.70	18.30
Rural	65	13.33	3.56	0.44	12.45	14.22	6.10	18.90

TABLE 2. *Duration of disease evolution depending on gender and origin*

Characteristics	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min years	Max years
					Lower Bound	Upper Bound		
Sex								
Male	63	5.40	3.60	.45	4.50	6.31	1.00	14.70
Female	56	4.90	2.96	.40	4.11	5.70	1.00	10.30
Origin								
Urban	54	5.25	3.06	0.42	4.41	6.09	1.00	11.50
Rural	65	5.10	3.52	0.44	4.23	5.97	1.30	14.70

TABLE 3. *The relationship between HbA1c and age group, age of diabetes, gender, origin*

Characteristics	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min %	Max %
					Lower Bound	Upper Bound		
Gender								
Male	63	8.63	1.87	0.24	8.15	9.10	5.16	15.15
Female	56	9.46	2.24	0.30	8.85	10.07	5.94	16.29
Origin								
Urban	54	9.09	2.32	0.32	8.45	9.73	5.35	16.29
Rural	65	8.96	1.89	0.24	8.49	9.43	5.16	14.41
Age group								
< 13 years	52	8.80	1.67	0.23	8.33	9.26	5.35	14.41
≥ 13 years	65	9.20	2.37	0.29	8.61	9.78	5.16	16.29
Age of diabetes								
< 5 years	64	9.02	1.94	0.24	8.54	9.51	5.80	15.15
≥ 5 years	53	9.02	2.27	0.31	8.39	9.64	5.16	16.29

p = 0.416) regardless of the origin (U 5.25 years vs. R 5.10 years; p = 0.806) (Table 2).

During monitoring, glycosylated hemoglobin (HbA1c) recorded average values ranging from 5.16% to 16.29%, the mean value being significantly higher in females (F 9.46% vs. M 8.63% p = 0.031). No significant differences were observed between the means of origin (Urban 9.09% vs. Rural 8.96%; p = 0.738), age groups (<13 years 8.80% vs. ≥13 years 9.20%; p = 0.309) or age of diabetes (<5 years 9.02% vs ≥5 years 9.02%; p = 0.986) (Table 3).

However, there is a direct correlation, moderate in intensity, between HbA1c level and child age (r = + 0.277; p = 0.002), 27.7% of children having a higher level of HbA1c at older ages (Figure 1).

The study shows that 28.6% of patients (34 cases) presented severe hypoglycemia, without significant differences in the estimated risk between the sexes (RR = 1; p = 1,000), but with a slightly higher risk in children from urban areas (RR = 1.25; 95% CI: 0.84-1.87; p = 0.315) and in those aged over 13 years (RR = 1.14; 95% CI: 0.82-1.59; p = 0.541).

In patients with diabetes for more than 5 years, the estimated risk of severe hypoglycemia was approximately 2-fold higher (RR = 1.92; 95% CI: 1.32-2.78; p = 0.002) (Table 4).

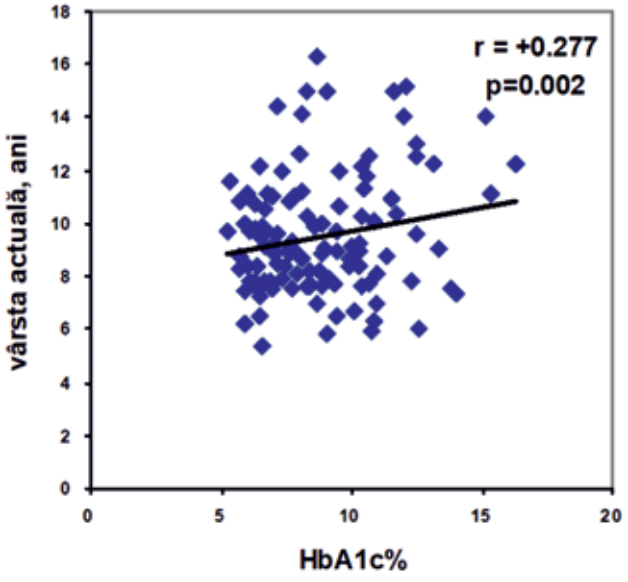

FIGURE 1. *The correlation between HbA1c and the child's age*

Among the most common causes of severe hypoglycemia is intense physical activity without additional carbohydrate intake in 15 cases, delayed carbohydrate intake in 11 cases, and insulin excess in 8 cases.

Regarding ketoacidosis, it was found in 15.13% of patients (18 cases), with an estimated risk slightly high-

er in females (RR = 1.52; 95% CI: 1.02-2.25; p = 0.122), in those with rural origin (RR = 1.28; 95% CI: 0.88-1.87; p = 0.309) and in adolescents aged over 13 years (RR = 1.34; 95% CI : 0.95-1.87; p = 0.199). In patients with diabetes for more than 5 years, the estimated risk of ketoacidosis was 1.63-fold higher (RR = 1.63; 95% CI: 1.09-2.43; p = 0.044) (Table 5).

TABLE 4. *Statistical significance of the patients with severe hypoglycemia*

	Patients with severe hypoglycemia	P	RR	IC95%
Male (n=63)	18 (28.6%)	1.000	1.00	0.69-1.46
Female (n=56)	16 (28.6%)		1.00	0.66-1.53
Urban (n=54)	18 (33.3%)	0.315	1.25	0.84-1.87
Rural (n=65)	16 (24.6%)		0.82	0.55-1.22
Age < 13 years (n=52)	13 (25.0%)	0.541	0.83	0.51-1.35
Age ≥ 13 years (n=67)	21 (31.3%)		1.14	0.82-1.59
Age of diabetes < 5 years (n=66)	11 (16.7%)	**0.002**	0.50	0.30-0.83
Age of diabetes ≥ 5 years (n=53)	23 (43.4%)		1.92	1.32-2.78

TABLE 5. *Statistical significance of the patients with ketoacidosis*

	Patients with ketoacidosis	P	RR	IC95%
Male (n = 63)	6 (9.7%)	0.122	0.60	0.30-1.17
Female (n = 56)	12 (21.4%)		1.52	1.02-2.25
Urban (n = 54)	6 (11.1%)	0.309	0.69	0.35-1.38
Rural (n = 65)	12 (18.8%)		1.28	0.88-1.87
Age < 13 years (n = 52)	5 (9.8%)	0.199	0.60	0.28-1.31
Age ≥ 13 years (n = 67)	13 (19.4%)		1.34	0.95-1.87
Age of diabetes < 5 years (n = 66)	6 (9.2%)	**0.044**	0.57	0.29-1.11
Age of diabetes ≥ 5 years (n = 53)	12 (22.6%)		1.63	1.09-2.43

Among patients with ketoacidosis, 55.55% (10 cases) had recurrent ketoacidosis, being in 39% of cases adolescents with a disease duration of more than 5 years, with low adherence to treatment and a precarious glycemic balance. In this regard, the presence of increased glycosylated hemoglobin was observed in all patients with recurrent ketoacidosis, thus demonstrating the link between unsatisfactory glycemic control and the occurrence of ketoacidosis.

In this study, because the majority of patients 87% (103 cases) followed a basal-bolus treatment regimen, no comparison could be made between the groups on glycemic balance and the frequency of acute metabolic complications depending on insulin treatment. Ketoacidosis was caused in 10 cases (55.5%) by major deviations from diet and additional carbohydrate intake, and in 8 cases (45.5%) by the omission of insulin doses. Among the factors favoring the appearance of acute metabolic complications, we also mention psychological disorders, these being identified in 17 patients (14.4%). Of these, during monitoring, 8 patients (47.1%; p = 0.005) had severe hypoglycemia and 7 patients (41.2%; p = 0.004) ketoacidosis.

DISCUSSIONS

Taking into consideration all the results we have obtained they can be compared to data from the literature that emphasizes the causal factors on severe hypoglycemia and ketoacidosis. In an 18-month study of a group of 142 children and adolescents with type 1 diabetes, Wysocki et al. reported a 41% incidence of severe hypoglycemia (15), while Rewers et al. found a frequency of 19% (16). According to some other data from, it is demonstrated a positive correlation between the age of the disease and hypoglycemia (17) and at the same time a causal relationship between severe hypoglycemia and delayed meals or snacks in 44% of cases (18).

As we showed in our results, inadequate glycemic control and the occurrence of ketoacidosis are strongly linked. In an international study of 49,859 pediatric patients with type 1 diabetes, Maahs et al. showed an increase in the frequency of ketoacidosis in patients with a Hb A1c value between 7.5% and 9% (19). Regarding the insulin therapy regimen used, the DCCT study showed that intensive insulin therapy (multiple daily insulin injections or an insulin pump) provides better glycemic control than conventional treatment with 2 or 3 injections per day (20). Wei-Yu Chou et al. observed a better value of Hb A1c in intensively treated patients than in the conventionally treated group, therefore explaining the low risk for ketoacidosis in patients with intensive insulin therapy. The same authors showed that the risk of ketoacidosis was significantly higher only in patients with Hb A1c values ≥ 7.5% (21). Approximately 28% - 65% of ketoacidosis occurs due to the omission of insulin doses, which is also the major cause of this complication in patients with type 1 diabetes (22-25). Furthermore, the need for periodic psychological and neurological evaluation is very important in the task of monitoring of type 1 diabetes in children and adolescents (26,27).

CONCLUSIONS

Managing pediatric patients with type 1 diabetes can be considered a real challenge. Achieving therapeutic goals (immediate and long-term) is mainly influenced by maintaining a euglycemic status, with blood glucose values as close as possible to normal values.

The diabetic child and adolescent may present, during the evolution of the disease, major variations of serum glucose with the appearance of acute metabolic imbalances, respectively ketoacidosis, and severe hypoglycemia. These are, in most cases, determined by low compliance with the recommended therapeutic means (insulin therapy, specific diet, physical activity, glycemic monitoring) and by the lack of involvement and awareness on the part of the patient. Severe hypoglycemia and ketoacidosis have immediate effects, through the vital prognosis, but also distant effects on the functionality of the nervous system in case of severe hypoglycemia.

In conclusion, it is fundamental to prevent these complications through continuous medical education of diabetic patients and their families.

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