# HYPOGLYCEMIA IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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## Abstract

***Background:*** *Hypoglycemia represents the most frequent acute complication which occurs in type 1 diabetes mellitus. The importance of hypoglycemia in the practice of pediatrics is given by the impact on neural development. The objective of this study is to identify the main factors which predict the sudden drop of glycemia – modifiable factors which may represent therapeutic targets for the prevention of this acute complication of diabetes mellitus.* ***Material and method:*** *The study included 52 children with type 1 diabetes mellitus, hospitalized in the Clinic III of Pediatrics, the "Sf. Maria" Emergency Clinical Hospital for Children, from Iasi, over the period January 2009 – December 2010. The inclusion criteria were: the diagnosis of severe hypoglycemia upon hospitalization; nocturnal hypoglycemia during hospitalization. The glycemia of the patients was monitored and they were assessed from the perspective of clinical (age, sex, duration of diabetes mellitus) and paraclinical (quality of long term glycemic control, insulin dose for 24 hours, insulin treatment scheme) parameters that may be involved in the occurrence of hypoglycemia.* ***Results:*** *Of the 52 patients with type 1 diabetes mellitus, 18 children suffered from severe hypoglycemia, whereas the other 34 children presented hypoglycemic episodes of moderate or mild intensity. The severity of hypoglycemia depends on the duration of diabetes mellitus, the degree of metabolic control and age. There were no statistically significant differences with regard to the patients' sex. As concerns the necessary dose of insulin, there was no statistically significant difference between the two groups, but the closest correlation with insulin is related to the number of injections per day ($p<0.05$). The prevalence of nocturnal hypoglycemia was 47%, of which 39% were symptomatic. The risk factors of nocturnal hypoglycemia were: at least two episodes of severe hypoglycemia from the onset of diabetes mellitus; insulin in a dose with >0.85 U/kilo body/day; over 5% of the measurements of glycemia ≤60 mg/dl during the last month of monitoring. The risk decreased with the age. Highly predictive values, with a relatively significant risk, were the threshold values of glycemia ≤90 mg/dl at dinner and ≤120 mg/dl at 7.00 AM.* ***Conclusions:*** *The recurrence of severe hypoglycemia in children with type 1 diabetes mellitus is determined by age, the duration of diabetes mellitus, long term glycemic control. The prediction is important for the increase of the quality of life of these patients and for the improvement of psychosocial comfort.*

***keywords:*** *type 1 diabetes mellitus in children, hypoglycemia, prediction factors.*

The adequate glycemic control, with normal values of the glycemia and of the glycolized hemoglobin, delays or prevents the occurrence of micro- and macrovascular complications. The DCCT study showed that, in patients with type 1 DM, intensive insulin treatment reduced the rate of occurrence and the progression of microvascular complications by approximately 60%. The price paid for attaining these objectives was the increase of the incidence of hypoglycemia, especially of the severe one. In the DCCT study, the incidence of hypoglycemia was three times bigger in the group with intensive treatment, in comparison with the group of patients who received conventional treatment [1].

Hypoglycemia represents the most frequent acute complication which occurs in type 1 diabetes mellitus. A glycemia value below 40mg% in infants and below 65mg% in children and teenagers is considered hypoglycemia. The statistical reporting of hypoglycemia is extremely difficult. The true prevalence of hypoglycemia is not known because the minor or average episodes are not reported or remain unknown. In a study with continuous monitoring of blood sugar, conducted on persons with type 1 DM, unconscious hypoglycemia is frequent, has an extended duration, is associated with bedtime glycemia ≤100-150mg/dl and the most frequent episodes occur between 9 pm and 1 am [2].

The importance of hypoglycemia in the practice of pediatrics is given by the impact on neural development. The privation of the brain of a major energy source (blood sugar) and the limiting of the use of alternative energetic substances due to hyperinsulinemia have severe consequences on brain metabolism. Average hypoglycemia can lead to neuropsychic anomalies: the reduction of the motive and intellectual performances (attention, memory etc). Although these anomalies are transitory, they can lead to disturbances in the school and social activity. Severe, prolonged, recurrent hypoglycemia determines final EEG anomalies, especially in small children.

Given these characteristics of hypoglycemia in type 1 diabetes mellitus in children, the objective of this study is to identify the main predictive factors for the sudden drop of glycemia. These modifiable factors can represent therapeutic targets for the prevention of this acute complication of diabetes mellitus.

## Material and method

The study included 52 children with type 1 diabetes mellitus, hospitalized in the Clinic III of Pediatrics, the "Sf. Maria" Emergency Clinical Hospital for Children, from Iasi, over the period January 2009 – December 2010. The inclusion criteria were:

– the diagnosis of severe hypoglycemia upon hospitalization,
– nocturnal hypoglycemia during hospitalization.

The characteristics of hypoglycemia were assessed according to the ADA recommendations [3]:

– severe hypoglycemia – an episode which required the help of another person for the administration of carbohydrates or glucagon. These episodes are associated with neuroglycopenia which may induce coma,
– documented symptomatic hypoglycemia – an episode with typical symptoms of hypoglycemia, accompanied by glycemia <70mg/dl,
– asymptomatic hypoglycemia – an episode which is not accompanied by typical symptoms of hypoglycemia, but the glycemia is below 70mg/dl,
– probable symptomatic hypoglycemia – an episode with symptoms of hypoglycemia, but which could not be objectified by measuring the glycemia,
– relative hypoglycemia – an episode described by the patient, with typical symptoms of hypoglycemia, but the glycemia >70mg/dl. This category includes patients with poor glycemia control who may have hypoglycemia symptoms at glycemia values over 70mg/dl.

The glycemia of all the patients was monitored, via complete profile, including at 3 am, and they were assessed from the perspective of clinical (age, sex, duration of diabetes mellitus) and paraclinical (quality of long term glycemic control, insulin dose for 24 hours, insulin treatment scheme) parameters that may be involved in the occurrence of hypoglycemia.

## Results

Of the 52 patients with type 1 diabetes mellitus, 22 were males and 30 females. The average age of the subjects was of 12.3 ±2 years, with variations between 8 and 14 years. The duration of DM varied between 5 and 10 years, with an average of 6.5 ± 2.4 years (table 1).

**Table 1. Characteristics of the group**

| | **N = 52** |
|---|---|
| Sex (M/F) | 22/30 |
| Age | 12.3 ± 2 years |
| Duration of type 1 diabetes mellitus | 6.5 ± 2.4 years |

In the study, 18 children suffered from severe hypoglycemia, whereas the other 34 children presented hypoglycemic episodes of moderate or mild intensity. In order to determine the predictive factors of the hypoglycemic severity, the patients were divided into two groups:
– Group 1 – comprised of 18 patients with severe hypoglycemia,
– Group 2 – comprised of 34 patients with episodes of mild or moderate hypoglycemia.

The patients were comparatively assessed from the perspective of the following parameters:
– duration of the diabetes mellitus,
– HbA1c,
– necessary dose of insulin for 24 hours,
– insulin treatment scheme,
– age,
– sex.

One may notice that the severity of hypoglycemia depends on the duration of diabetes mellitus, on the degree of metabolic control and on the age. There were no statistically significant differences with regard to the patients' sex. As concerns the necessary dose of insulin, there was no statistically significant difference between the two groups and the closest correlation with insulin is related to the number of daily injections:

severe hypoglycemia was more frequent in patients with several injections per day (p<0.05) (figure 1).

**Table 2. Clinical and paraclinical parameters in severe hypoglycemia**

| Parameter | Group 1 (n=18) | Group 2 (n=34) | Value P |
|---|---|---|---|
| Duration of the disease | 5.7±1.3 years | 3.3±2.5 years | P<0.05 |
| HbA1c | 7.45 ± 1.75% | 9.22 ± 1.78% | P<0.05 |
| Necessary dose of insulin | 0.82±0.27 U/kg | 0.88±0.5 U/kg | Insignificant |
| Age | 8±1.7 years | 10±2.5 years | P<0.05 |
| Sex (male %) | 55% | 58% | Insignificant |

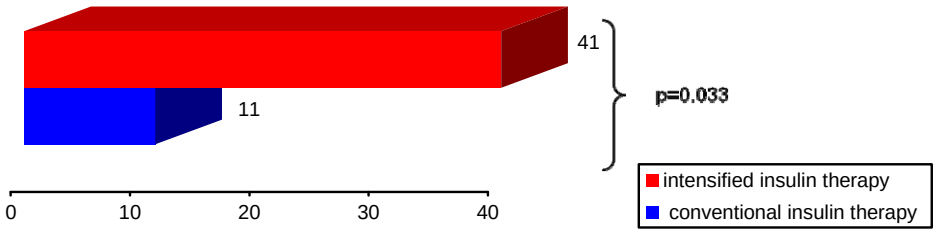


**Fig. 1.** Severe hypoglycemia vs. insulin treatment scheme

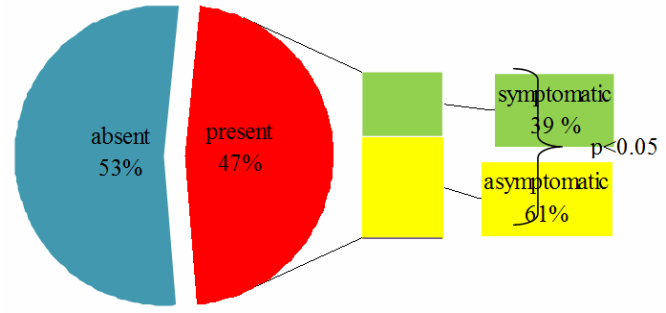


**Fig. 2.** Nocturnal hypoglycemia

In children and teenagers with type 1 DM, the prevalence of nocturnal hypoglycemia (objectified via glycemia <65mg/dl at 3 a.m.) was 47%, of which 39% were symptomatic (figure 2).

**Table 2. Estimate of the opportunity and risk parameters of nocturnal hypoglycemia vs. threshold values of glycemia at dinner and at 7**

| | Estimated value | *95% Confidence interval* | |
|---|---|---|---|
| | | Minimum | Maximum |
| Opportunity PARAMETERS | | | |
| Opportunity ratio (OR) | 5.23 | 4.87 | 9.20 |
| Risk PARAMETERS | | | |
| Risk ratio (RR) | 5.67 | 3.63 | 7.85 |

The risk factors of nocturnal hypoglycemia were:

– at least 2 episodes of severe hypoglycemia from the onset of diabetes mellitus,

– insulin in a dose of >0,85 U/kilos per body/day,
– over 5% of the measurements of glycemia ≤60mg/dl during the last month of monitoring.

The risk decreased with the age. Highly predictive values and with relatively significant risks were the threshold values of glycemia ≤90mg/dl at dinner and ≤120mg/dl at 7 a.m. For the values of glycemia at 10 p.m, the prediction concerning nocturnal hypoglycemia was weak (table 2).

## Discussions

Hypoglycemia is a common complication in insulin treatment, especially in young patients. For children and teenagers with diabetes mellitus, the risk of hypoglycemia may be a factor which resists optimum glycemic control and, at the same time, a psychosocial stress of the disease. Generally, persons with type 1 diabetes mellitus usually have around two episodes of symptomatic hypoglycemia per week [4]. When glycemia drops, a sequence of responses of counter regulation is triggered; this sequence mainly involves the release of some hormones of counter regulation which act rapidly in order to stimulate the production of endogenous blood sugar and to restrict the peripheral use of blood sugar. When the levels of glycemia drop even further, the fact that the patient subjectively becomes aware of hypoglycemia leads to a series of behavior modifications. In healthy subjects, this homeostatic mechanism functions well and the episodes of hypoglycemia are rare, but in the case of persons suffering from type 1 diabetes mellitus these compensatory systems are disturbed at each level.

The study has shown that the severity of hypoglycemia significantly depends, from a statistical perspective, on the duration of the disease: the group of patients with severe hypoglycemia had an average duration of diabetes mellitus of 5.7 years, with variations between 5 and 9 years. From the perspective of its evolution, type 1 diabetes mellitus is characterized by failures of the system of defense against hypoglycemia via the counterregulatory hormones. Within 5 years from the diagnosis of type 1 diabetes mellitus, hypoglycemia no longer manages to determine the stimulation of the release of glucagon, the main counterregulatory hormone [5]. Consequently, young people with type 1 diabetes mellitus are dependent primarily on the symptomatic and adrenergic response (on adrenaline and noradrenaline) to low glycemia. However, within a ten years' interval from the diagnosis, in most patients there also occur other disorders of the sympatoadrenergic response and of other neuro-hormonal responses to hypoglycemia [6]. During the evolution of type 1 diabetes mellitus, one may notice the fact that the patients become aware of the symptoms. This combination of physiological and behavioral responses, altered in the case of hypoglycemia, significantly increases the risk of severe hypoglycemia in children with type 1 diabetes mellitus.

Age was associated with an increased risk of severe hypoglycemia, especially in smaller children. As children grow, they acquire important elements of specific education, the child becoming more aware of the condition it suffers from and, thus, the incidence of severe hypoglycemia decreases with the age. The high risk of severe hypoglycemia depends on

the evolution and age of the child with diabetes mellitus, phenomenon also proven by the DCCT trial [7]. In children and teenagers with diabetes mellitus, the small values of glycolized hemoglobin were statistically significant associated with a considerable risk of severe hypoglycemia. After the first year of evolution of diabetes mellitus, HbA1c values smaller than 8% require intensive insulin treatment and represent an important predictive factor for hypoglycemia [8].

The study showed a higher frequency of nocturnal hypoglycemia of which patients are not aware, with a longer duration than daytime hypoglycemia and more difficult to identify by the subject. Most nocturnal hypoglycemic episodes (61%) occurred in children who did not have a snack. Nocturnal hypoglycemia is usually asymptomatic, but it determines the diminution of the quality of life the following day and leads, in the short term, to the failure to notice hypoglycemia [9]. Not being aware of hypoglycemia represents a major risk factor for the occurrence of severe hypoglycemia in children with diabetes mellitus [10]. Nocturnal hypoglycemia in children and teenagers with type 1 DM was more frequent after a glycemic value of <90mg/dl at dinner, but it also frequently appeared in subjects with glycemia >180mg/dl. The glycemic values at bedtime have a very small predictive value for the hypoglycemia in the following night. None of the glycemic values at bedtime reduced the risk of nocturnal hypoglycemia below 10% [11]. In a study conducted on children with type 1 diabetes mellitus, treated with a conventional insulin regime, asymptomatic nocturnal hypoglycemia was frequent and could be correlated with the dose of insulin, but not with the glycolized hemoglobin, and is partially predicted by the glycemia <130mg/dl at 0.00 [12].

It is worth mentioning that nocturnal hypoglycemia occurred more frequently during the nights preceded by physical exercise. The disorders of the counterregulatory hormones, which occur during sleep, lead to the increase of the risk of hypoglycemia throughout the entire night in patients with type 1 diabetes mellitus [13]. Asymptomatic nocturnal hypoglycemia determined the reduction of the identification threshold of hypoglycemia and reduced the magnitude of the neuroglycopenic and autonomous symptoms, the response of the counterregulatory hormones and the cognitive function. All these data suggest the involvement of nocturnal asymptomatic hypoglycemia in the failure to notice hypoglycemia and this explains why not every patient with this disorder has a history of hypoglycemia [14].

## Conclusions

This study confirmed the fact that hypoglycemia is a recurrent problem in children with type 1 diabetes mellitus. Recurrence is determined by age, by the duration of diabetes mellitus and by long term glycemic control. The presence of previous hypoglycemic episodes may help identify patients with high risk of occurrence of these acute complications. The prediction of severe hypoglycemia in children with diabetes mellitus is important for the increase of the quality of life of these patients and for the improvement of psychosocial comfort.

Hypoglycemia inevitably occurs in the case of low HbA1c values. Due to the frequent occurrence of hypoglycemia in children and

young persons with type 1 diabetes mellitus, it is important to accurately identify and correct the factors which cause hypoglycemia for this category of persons. Consistent glycemic monitoring, the establishing of some secure targets with short, as well as long term impact, the control of risk factors are efficient methods for the prevention of this acute complication of diabetes mellitus.

## REFERENCES


**1. The Diabetes Control and Complications Trial Research Group**. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med* 329: 977-986. 1993.

**2. Kaufman FR et al**. Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. *J Pediatr* 1993, 141(5): p. 625-30; 2002.

**3. Workgroup on Hypoglycemia, American Diabetes Association**. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 28: 1245; 2005.

**4. Graham P, Leese, Jixian Wang, Janice Broomhall et al.** Frequency of Severe Hypoglycemia Requiring Emergency Treatment in Type 1 and Type 2 Diabetes. *Diabetes Care* 26(4): 1176- 1180; 2003.

**5. Mokan M, Mitrakou A, Veneman T, Ryan C, Korytkowski M, Cryer P, Gerich J.** Hypoglycemia unawareness in IDDM. *Diabetes Care* 17: 1397-1403; 1994.

**6. Mokan M, Mitrakou A, Veneman T, Ryan C, Korytkowski M, Cryer P, Gerich J.** Hypoglycemia unawareness in IDDM. *Diabetes Care* 17: 1397-1403; 1994.

**7. Diabetes Control and Complications Trial Research Group.** Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med* 90: 450-459; 1991.

**8. Chase HP, Lockspeiser T, Peery B, et al.** The impact of the diabetes control and complications trial and humalog insulin on glycohemoglobin levels and severe hypoglycemia in type 1 diabetes. *Diabetes Care* 24: 430-434; 2001.

**9. DeVries, J.H. et al.** Nocturnal hypoglycaemia in type 1 diabetes-consequences and assessment. Diabetes *Metab Res Rev* 20(Suppl 2): S43-6; 2004.

**10. Holstein AA. Plaschke and Egberts EH.** Clinical characterisation of severe hypoglycaemia--a prospective population-based study. *Exp Clin Endocrinol Diabetes* 111(6): 364-9; 2003.

**11. Wiltshire EJ, Newton K and McTavish L.** Unrecognised hypoglycaemia in children and adolescents with type 1 diabetes using the continuous glucose monitoring system: prevalence and contributors. *J Paediatr Child Health* 42(12): 758-63; 2006.

**12. Matyka KA et al.** Cognitive function and mood after profound nocturnal hypoglycaemia in prepubertal children with conventional insulin treatment for diabetes. *Arch Dis Child* 81(2): 138-42; 1999.

**13.** Impaired overnight counterregulatory hormone responses to spontaneous hypoglycemia in children with type 1 diabetes. *Pediatr Diabetes* 8(4): 199-205; 2007.

**14. Veneman, T et al.** Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes* 42(9): 1233-7; 1993.



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