Effect of Education on Impaired Hypoglycemia Awareness and Glycemic Variablity in Children and Adolescents with Type 1 Diabetes Mellitus.

Short title: CGM and hypoglycemia unawareness and Type 1 Diabetes Mellitus

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What is already known in this topic?
Impaired hypoglycemia awareness and glycemic variability are important problems causing acute and chronic complications in children and adolescents with type 1 diabetes.

What this study adds?
Professional continuous glucose measurement system is a valuable tool to diagnose impaired hypoglycemia awareness in type 1 diabetic children and adolescents. IHA, GV and time in range can be improved by education-based intervention.

Abstract
Objective: The aim of this study was to determine the prevalence of impaired hypoglycemia awareness (IHA) in children and adolescents with type 1 diabetes mellitus with professional continuous glucose monitoring system and to show the effect of structured education on glycemic variability (GV) in children and adolescents with IHA.
Methods: Fourty type 1 diabetic children and adolescents with a diabetes duration of at least 5 years were eligible for inclusion in this prospective, quantitative study. All subjects were asked about their history of being aware of the symptoms of hypoglycemia with a questionnaire. Professional continuous glucose monitoring (CGM) were placed to all of the patients for six days. The frequency of IHA detected by CGM and logbook reports were analyzed. Patients with IHA diagnosed by CGM underwent a structured training program. After 3 months, CGM was re-applied to patients with IHA.
Results: The study was completed by 37 diabetic children and adolescents. After the initial CGM nine patients (24.3%) were determined to have had episodes of IHA. Area under the curve (AUC) for hypoglycemia and number of low excursions were; 1.81±0.95 and 8.33±3.60 for the IHA group at the beginning of the study. AUC for hypoglycemia was 0.43±0.47 after three months of structured education the IHA patients (p=0.01). Coefficient of variation (CV) which shows primary glycemic variability decreased significantly although unstable at the end of education in IHA patients (p=0.03).
Conclusion: CGM is a valuable tool to diagnose impaired hypoglycemia awareness. IHA, GV and time in range can be improved by education-based intervention.
Keywords: Continuous glucose monitoring, education, impaired hypoglycemia awareness, glycemic variability, type 1 diabetes, children

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Introduction

Hypoglycemia is the most common acute complication of type 1 diabetes with adverse effects on both the quality of life of patients and the management of their diabetes (1,2) Hypoglycemia is usually defined as a plasma glucose level <70 mg/dl (3.9 mmol/L) (3). The following classifications of hypoglycemia, based on clinical evaluation, is offered. Level 1: a hypoglycemia alert glucose value of <70–54 mg/dL (3.9–3.0 mmol/L) with or without symptoms. Level 2: a glucose level of <54 mg/dL (3.0 mmol/L) with our without symptoms. This should be considered clinically significant hypoglycemia requiring immediate attention. Level 3: severe hypoglycemia. This denotes cognitive impairment requiring external assistance for recovery but is not defined by a specific glucose value (4). The main symptoms of hypoglycemia occur as a result neuroglycopenic and autonomic activation (5). Neuroglycopenic symptoms occur as a result of hypoglycemic activation of the autonomic nervous system and these symptoms are often severe enough that hypoglycemia will be noticed by the patient, thus providing protection from complications related to hypoglycemia (6). Nocturnal hypoglycemia is often asymptomatic and mild hypoglycemia during the day may not be noticed by the patient. Therefore it is difficult to determine the true

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frequency of hypoglycemia. As efforts to achieve optimal glucose control increase in order to prevent the chronic complications of diabetes, the risk of hypoglycemia increases. Recurrent antecedent hypoglycemia induces sympathoadrenal responses and unawareness of hypoglycemia (6-10). This is known as impaired hypoglycemia awareness (IHA) and can be defined as the inability to perceive the onset of hypoglycemia. Typically, autonomic symptoms are lost before neuroglycopenic symptoms, which then predominate (3). Type 1 diabetic patients with IHA and impaired counter-regulation are more likely to suffer from severe hypoglycemia, have longer diabetes duration and, interestingly, lower HbA1c. The perception of adrenergic symptoms are reduced or disappear completely (6,7). It has been reported that careful glucose monitoring, individualized blood glucose targets and structured education programs are important in preventing and managing IHA (6-10). Real time continuous glucose monitoring systems reduce IHA in children, adolescents and adults with type 1 diabetes (6,10). The aim of this study was to determine the prevalence of IHA in children and adolescents with type 1 diabetes mellitus attending a single center with professional continuous glucose monitoring system and to show the effect of structured education on glycemic variability in children and adolescents with IHA. Impaired hypoglycemia awareness (IHA) is a major limitation to achieving tight metabolic control of type 1 diabetes and reduced quality of life.

Methods

Type 1 diabetic children and adolescents with a diabetes duration of at least 5 years were eligible for inclusion in this prospective, quantitative study. Patients were selected regardless of their metabolic control. The study was approved by the Ege University Medical Ethics Committee (Approved number: 14-7/15). Written, informed consent was obtained from all participants and their parents.

All subjects were asked about their history of being aware of the symptoms of hypoglycemia prior to starting continuous glucose monitoring (CGM) with the following question: "Do you feel the symptoms of hypoglycemia". Possible answers were: "yes", "no" or "sometimes". All subjects and their parents were invited to the outpatient clinic for a two hour training and evaluation session. CGM sensors used for all subjects were Medtronic iPro®2 professional continuous glucose monitoring system (MiniMed Medtronic; Northridge). Sensor placement was performed by one of the Diabetes Educators. Calibration of the sensor was accomplished by following the protocol established and outlined in the MiniMed CGM manual.

During continuous glucose monitoring, patients and parents were asked to measure a minimum of four finger-stick blood glucose levels per day and to record glucose values, meals, insulin doses, exercise periods and symptomatic hypoglycemia in a logbook. Patients used the same brand of glucometer during the monitoring period (Accuchek performa Nano Roche Diagnostics).

At the completion of the six-day CGM period, the system was returned and the data downloaded to determine glucose patterns together with data from the logbooks. Glucose data from each day were analyzed at two different time periods: day and night. Responses to hypoglycemia and exercise, the presence of unrecognized hypoglycemia and the number of high and low patterns seen with the CGM were evaluated from the information collected. Hypoglycemia was defined as the values below 70 mg / dl of glucose. Patients noted the events of symptomatic hypoglycemia occurring in 6 days. These notes were compared with the data obtained from CGM.

Data on mean annual HbA1c values were obtained from medical records. HbA1c was measured by turbidimetric inhibition immunoassay (Roche Cobas c513 analyzer using the Tina quant® HbA1c Gen. 3 assay) before the monitoring period and three months after modifications were made.

The frequency of IHA detected by CGM and logbook reports were analyzed. Patients with IHA diagnosed by CGM underwent a structured training program (administration of insulin, hypoglycemia training, safe exercise management and ideal blood sugar levels) and the patients were seen weekly for three months. More frequent capillary blood glucose measurements were performed (4 to 6 times daily). After 3 months, CGM was re-applied to patients with IHA.

Statistical Analyses

Data were evaluated using Windows SPSS 16.0 statistical package program. Participants' gender, nutrition, hypoglycemia insensitivity and hypoglycemia insensitivity according to their sex status, duration of grouped diabetes and hypoglycemia insensitivity to diabetes, and hypoglycemia symptoms were analyzed by Chi-Square test. HbA1c levels before and after the study, the number of blood glucose measurements at the beginning of the study and the t-test for independent groups were used for the analysis of the CGM at the beginning of the study. Mann Whitney U test was used to analyze the baseline data of the participants. Wilcoxon sorting test was used for the analysis of the CGM data before and after the study. P value <0.05 was considered significant.

Results

Forty patients were recruited for the study. Three patients withdrew because of poor sensor compliance. Thus the study was completed by 37 diabetic children and adolescents. Mean ± standart deviation (SD) age of the patients and mean diabetes duration were 13.80±2.42 and 7.67±1.66 years respectively. 41% were male, 59% were female. Mean HbA1c was 8.0±1.2% in all the patients. 25 patients were on multiple daily insulin (MDI) therapy while the rest were on continuous subcutaneous insulin infusion (CSII) without sensor. No significant difference was found between CSII and MDI patients according to mean HbA1c at the start of therapy.

After the initial CGM nine (6 female/3 male) patients (24.3%) had episodes of IHA. Seven (77.7%) of the IHA patients were on MDI and the two were on CSII. Six (66.6%) of the IHA patients had relatively shorter duration of

diabetes of between five and eight years while the remainder had a longer duration ranging from eight to eleven years. Seven (77.7%) of the IHA patients had completed puberty; one was Tanner stage 3 and the other Tanner stage 1. Mean HbA1c and glucose levels of the patients with and without IHA within preceding year are given in table 1.

Eight (21.6%) of the patients diagnosed as IHA with CGM filled out the questionnaire as 'I always feel the symptoms' and one (2.7%) of the patients who answered the questionnaire as 'I sometimes feel the symptoms' were diagnosed as IHA with CGM. There were no significant correlation between the true presence of IHA and the declared awareness of hypoglycemia as given in the questionnaire responses.

IHA cases were hypoglycemic (blood glucose <70 mg/dl) for 11.44 ± 5.12 hours while patients without IHA were hypoglycemic for significantly less time at 1.93 ± 2.23 hours at the beginning of the study (p<0.01). Area under the curve (AUC) for hypoglycemia and number of low excursions were; 1.81 ± 0.95 and 8.33 ± 3.60 for the IHA group and significantly less as 0.23 ± 0.31 and 2.68 ± 2.05 for the others, respectively, at the beginning of the study (p<0.01).

In the patients with IHA the time spent < 70 mg for the postprandial periods were; 19.1% at breakfast, 27.6% at lunch, 24.4% at dinner, 25.4% between 20.00-24.00 hours and 34.6% between 24:00-07:00 hours.

After three months of structured education the IHA patients were hypoglycemic for 4.44 ± 3.78 hours, AUC for hypoglycemia was 0.43 ± 0.47 and the number of low excursions were 5.22 ± 3.99. Though AUC and hypoglycemia duration statistically decreased compared to the initial findings (p=0.01-p=0.00), the number of hypoglycemic excursions did not change with structured education. HbA1c levels in IHA patients increased from $7.93\pm0.90\%$ to $8.20\pm0.85\%$ with three month educational intervention although this was not statistically significant (p=0.35). When key metrics for CGM were assessed; AUC per 24 h (mg/dlxday) and time spent for level 1 and level 2 hypoglycemia and percentage of time spent in level 1 hypoglycemia decreased significantly with structured education. AUC per 24 h (mg/dlxday) and percentage of time spent in level 1 and 2 hyperglycemia did not change (Table 2 and 3). % of change in AUC (mg/dlxday) for level 1-2 hypo and hyperglycemia and time in range is given in figure 1. Level 2 hypoglycemia decreased by 80% while level 1 hypoglycemia increased by 12%, time in range increased by 17.7% (p<0.05). CV which shows primary glycemic variability decreased significantly although unstable at the end of three months with education in IHA patients (p:0.03) (Figure 2).

Discussion

Impaired hypoglycaemia awareness is defined as poor alertness to and therefore poor responsiveness to the signs and symptoms of hypoglycaemia (3). IHA is a major risk factor for serious hypoglycemia. A significant decrease in autonomic signs has been reported in even very brief periods of hypoglycemia in subjects with hypoglycemia unawareness (8).

IHA is reported frequently in adults with type 1 diabetes (11). In The Diabetes Control and Complications Trial study, 36% of serious hypoglycemia incidents were attributed to hypoglycemia unawareness (12). Cryer *et al.* and Pramming *et al.* reported loss of autonomic signs in 50% of type 1 diabetic adult patients with 15-20 years of duration in the questionnaire-based studies they conducted (13,14). Gold *et al.* detected IHA in 29 cases (48%) with a mean age of 48.4 ± 11.0 years and a mean duration of 21 ± 8 years (15). Hepburn *et al.* reported lower rates of IHA in 111 subjects out of 305 (36.4%) of type 1 diabetic patients in a questionnaire-based study (11).

However it is not clear whether frequency of IHA is the same among pre-pubertal children and adolescents. Gravelling *et al.* carried out a questionnaire study of 98 pediatric diabetic patients assessed by scale. They found hypoglycemia unawareness in 22 cases (22.4%) in subjects with a mean age of 8.2 (5.7-10.5) years and mean diabetes duration of 3.2 ± 2.0 years (8). In a large study of 650 children with type 1 diabetes mellitus which included a questionnaire, IHA was reported in 30% of subjects which is similar to results reported for adults with type 1 diabetes (16). In our study, IHA was detected in 24.3% of 37 children and adolescents with type 1 diabetes mellitus.

Davis *et al.* showed that sex is a risk factor because females are more likely to have a suppressed hormone response to hypoglycemia (17). It has been suggested that estrogen is an intermediary for this situation. In our study, 6 of the 9 of the IHA patients were female. 4 of the 6 female patients were at Tanner stage 5. Although the number of IHA patients is few to draw a conclusion about estrogen; female IHA patients were more than males.

Existence of a relation between high rates of serious hypoglycemia, the decreased ability to detect hypoglycemia together with prolonged duration of type 1 diabetes and development of IHA have been reported often in the adult literature (13-15,18-23). In our study, IHA was detected in patients with shorter disease duration (27.3%) compared to those patients with longer disease duration (20%). This may be due to the closer duration of diabetes in the two groups and shorter duration of diabetes than the adult studies.

The adoption of more flexible HbA1c targets, especially for diabetic patients that have a history of serious nocturnal hypoglycemia and diabetic patients unable to express hypoglycemic symptoms at younger ages in order to decrease the frequency of hypoglycemia is needed (6,24). The target value for HbA1c in the ISPAD guidelines is <7 %, regardless of patient age (25). However HbA1c levels are not an indicator for frequency of hypoglycemia. In our study, mean HbA1c and mean glucose levels were lower in the IHA group. Considering lower HbA1c values, mean blood glucose levels and continuous subcutaneous glucose monitoring data, presence of IHA has an association with reduced mean blood glucose levels and decreased HbA1c levels. Even though it was statistically

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insignificant, hypoglycemia unawareness tends to occur more frequently in the group with lower HbA1c levels.

In Type 1 Diabetes Exchange study serious hypoglycemia was lower in pump users (26). It was thought that insulin pump therapy decreased HbA1c without increasing hypoglycemia frequency and the risk of hypoglycemia unawareness (26). In our study only 2 of the 9 IHA patients were on pump therapy without sensors.

Gold *et al.* reported that participants usually experienced hypoglycemic symptoms in the morning. These patients stated the presence of neuroglycopenic symptoms during hypoglycemia (15). In our study, when subjects were asked the question "Do you experience hypoglycemia signs?", among subjects with hypoglycemia unawareness diagnosed with continuous subcutaneous glucose monitoring, 21.6% replied 'yes, I do experience'; 2.7% replied 'I sometimes experience'. Not one of the subjects said that they were unaware of hypoglycemia. According to continuous subcutaneous glucose monitoring data over 24-hours, it was evident that subjects who had IHA, mostly experienced hypoglycemia between 24.00-07.00 hours (34.6%) with a further 27.6% detected in the postprandial period at noon and this dropped further to 25.4% between 20.00-24.00 hours. Among subjects who did not experience IHA with continuous subcutaneous glucose monitoring, 54.1% said "I do experience" where 16.2% said "I do not experience". The difference between continuous subcutaneous glucose monitoring data and answers to the question "Do you experience hypoglycemia signs?" suggested that symptoms indicating hypoglycemia were not noticed, individuals' perceptions of indications were insufficient for detection of hypoglycemia, and individuals replied to the questionnaire based on their emotions at the time of survey rather than their true experience. Continuous subcutaneous glucose monitoring data is safer because of the elimination of subjective impressions and being reliably quantitative.

Avoiding hypoglycemia for three weeks is sufficient for the abolition of IHA and partial restoration of the adrenal response to hypoglycemia (6,22,27,28). In our study, hypoglycaemia awareness recovered at the end of a three month structured training programme which included hypoglycemia and insulin management, safe exercise management and increased target blood glucose levels.

In HypoCOMPaSS Trial GV was improved within 24 weeks in adults with long-standing type 1 diabetes complicated by IHA and recurrent sevre hypoglycemia with the help of education based intervention shown by blinded CGM (29). In the IN CONTROL study real time CGM increased time spent in normoglycaemia and reduced severe hypoglycaemia in adult patients with type 1 diabetes and impaired awareness of hypoglycaemia, compared with SMBG (30). In our study we have shown that in type 1 diabetes mellitus with structured education; frequency of level 2 hypoglycemia decreased with more time spent in normoglycemia; produced less glucose variability shown by decreased CV without a change in metabolic control assessed by HbA1c.

Study Limitation

The limitations of our study were that the follow-up period was short and the number of cases was low. Longer follow-up studies may be necessary.

In conclusion, we have shown that professional CGM is a valuable tool to diagnose impaired awareness of hypoglycemia and glycemic variability can be improved in pediatric type 1 diabetes patients complicated by IHA with the help of education-based intervention.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of Ege University Medical Ethics Committee (Approved number:14-7/15).

Informed Consent: Written, informed consent was obtained from all participants and their parents.

Authorship Contributions

Surgical and Medical Practices: Günay Demir, Samim Özen, Hafize Çetin, Damla Gökşen

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Conflict of Interest: No conflict of interest

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Table 1. HbA1c, diabetes duration, age and mean blood glucose levels of patients with and without IHA

	Diabetes duration (year)	Age (years)	HbA1c at the beginning (%)		Average sensor glucose (mg/dl)	
			CSII	MDT	CSII	MDT
With IHA (n=9)	7.63±1.45	14.82±2.13	7.25±0.35	8.13±0.94	134.2±21.3	169.4±19.2
Without IHA (n=28)	7.69±1.74	13.59±2,47	7.60±0,95	8.76±1.51	178.6±17.4	209.7±29.3
p	0.91	0.19	0.25		0.59	

Data were presented as mean ± standard deviation.
CSII: Continuous subcutaneous insulin infusion, IHA: Impaired hypoglycemia awareness, MDT: multiple daily injections

Table 2: Area under the curve (AUC) per 24 hours (mg/dl xday)

| Glucose levels	Before education	After education	p
< 54 mg/dl (Level 2)	302.5±2.6	68.8±116.6	0.01
54-70 mg/dl (Level 1)	94.2±7.3	105.7±6.9	0.004
70-180 mg/dl	321.4±39.7	450.4±55.5	0.02
180-250 mg/dl (Level 1)	111.2±47.0	162.5±73.3	0.08
> 250 mg/dl (Level 2)	50.5±32.9	86.0±11.4	0.17

Data were presented as mean ± standard deviation

Table 3: Percentage of time spent with glucose levels in specific glucose ranges

| Glucose levels	Before education	After education	p
< 54 mg/dl (Level 2)	5.1±3.3	0.6±0.9	0.008
54-70 mg/dl (Level 1)	6.7±3.6	4.2±2.8	0.13
70-180 mg/dl	30.4±11.3	31.2±15.0	0.51
180-250 mg/dl (Level 1)	22.1±7.0	26.2±8.0	0.08
>250 mg/dl (Level 2)	14.9±7.1	21.9±13.0	0.2

Data were presented as mean ± standard deviation

Figure 1: % change in area under the curve (mg/dLxday) after education for impaired hypoglycemia awareness

%
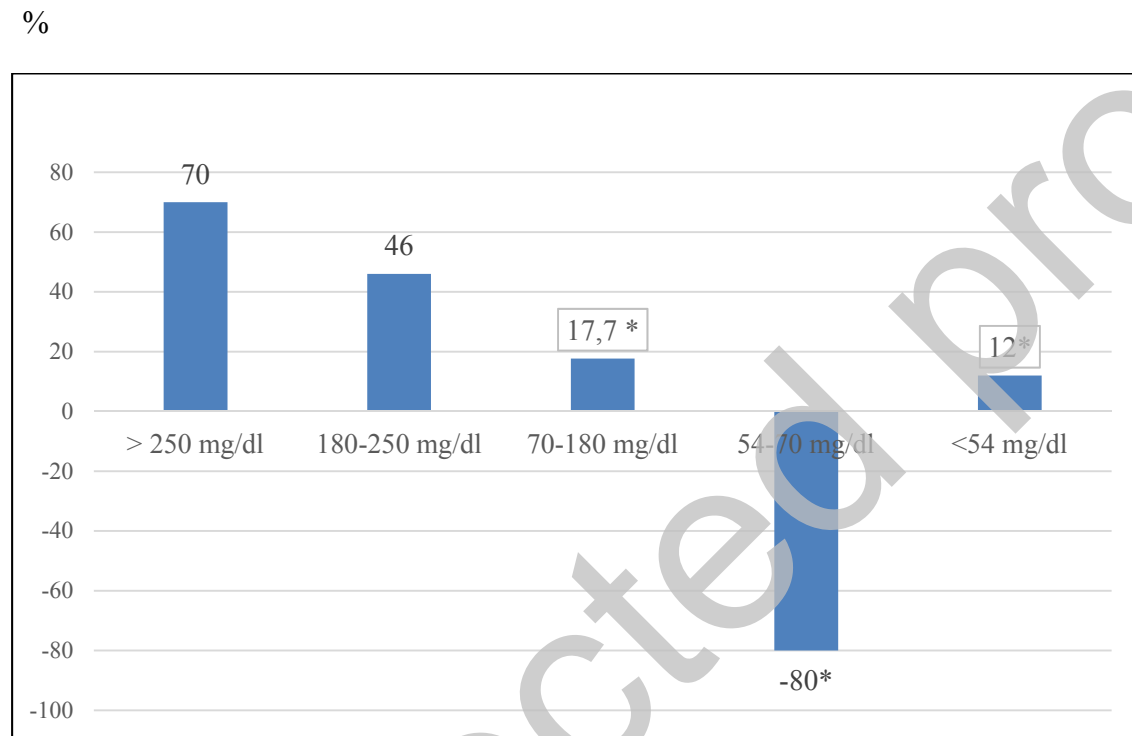
* p<0.05

Figure 2: Change in coefficient of variation after education for impaired hypoglycemia awareness
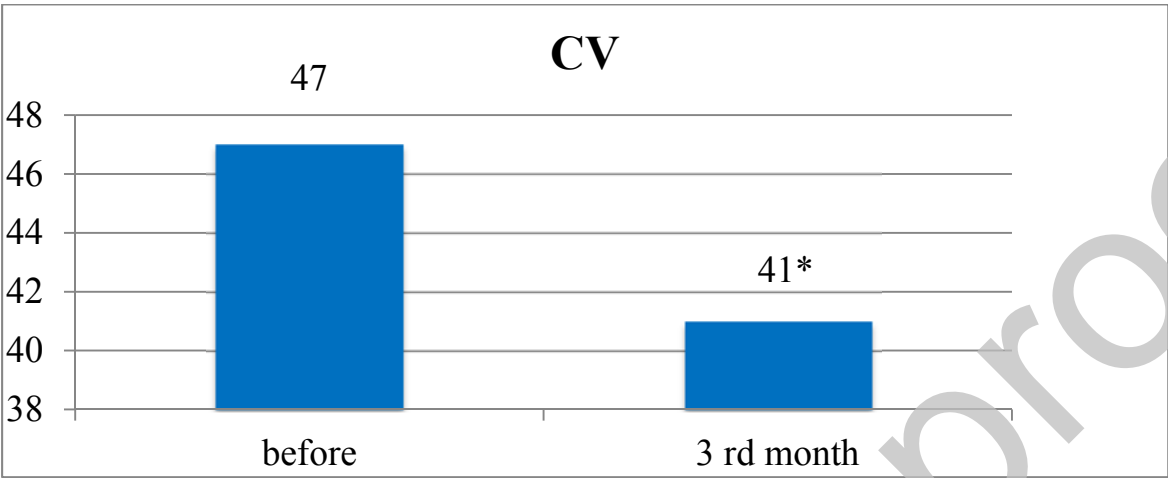
CV: coefficient of variation   *p=0.03