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ORIGINAL ARTICLE

Clinical factors affecting the perception of hypoglycemia in type 1 diabetes patients treated with personal insulin pumps

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Abstract

Introduction and Objective. The ability to perceive the symptoms of hypoglycemia during the early decrease in plasma glucose concentration may be critical for the safety of T1DM patients treated with intensive insulin therapy, including those treated with continuous subcutaneous insulin infusion (CSII). In the presented observational study an attempt was made to asses clinical factors that might affect subjective awareness of hypoglycemia in CSII-treated T1DM patients, with special attention to factors specific for this mode of treatment.

Materials and Methods. For the purpose of the study, data of 110 CSII-treated T1DM patients were collected (78 females and 32 males). The records were analyzed from glucose meters (200-300 measurements/download, depending on meter type) and insulin pumps (total insulin dose, basal/bolus ratio, number of boluses/day, bolus calculator and dual wave/square bolus usage, continuous glucose monitoring data) from the last 3 years.

Results. It was found that the level of subjective hypoglycemia perception inversely correlated with the number of hypoglycemic episodes per 100 measurements, age, duration of diabetes, time on insulin pump, and positively correlated with mean glycemia ($n = 98$; $r = 0.22$; $p = 0.0286$). With respect to CSII-related factors, hypoglycemia perception inversely correlated with the percentage of basal insulin ($n = 106$; $r = -0.20$; $p = 0.0354$). In stepwise regression analysis, independent predictors for impaired hypoglycemia perception were: age $\beta = -0.29$ ($p = 0.023$), duration of diabetes $\beta = -0.24$ ($p = 0.029$) and number of the hypoglycemia episodes for 100 measurements $\beta = -0.33$ ($p = 0.0005$).

Conclusions. Risk factors for impaired hypoglycemia perception in CSII-treated patients include those identified previously for the general population of T1DM individuals. In addition, the presented results suggest that a higher basal/bolus ratio may lead to impairment of the ability to perceive early symptoms of hypoglycemia.

Key words

insulin pump, continuous subcutaneous insulin infusion, diabetes, hypoglycemia perception

INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) showed that intensive insulin therapy in type 1 diabetes (T1D) combined with structured self-monitoring of blood glucose can delay the onset and slow down the progression of the microvascular complications of diabetes, compared to the conventional therapy [1]. Unfortunately, it has been shown that intensive insulin therapy may increase the risk of hypoglycemia [1, 2, 3], which is a major limiting factor in the management of diabetes.

The ability to perceive symptoms of hypoglycemia during the early decrease in plasma glucose concentrations, called hypoglycemia awareness, may be critical for the patient's safety and the prevention of severe hypoglycemic episodes, irrespective of the treatment mode [4]. Furthermore, impaired hypoglycemia perception may lead to hypoglycemia fear, which may result in behaviours purposefully elevating the patients' blood glucose levels [5]. It may also severely limit the patient's activities, as well as employment options [6].

Intensive insulin therapy may be implemented either with continuous subcutaneous insulin infusion (CSII) via a personal pump, or with a multiple daily injections (MDI) model. The currently available data suggest that in adults with T1D, CSII is more effective than MDI in optimizing glycemic control [7, 8, 9]. CSII was shown not only to prevent hypoglycemic episodes, but also to improve hypoglycemia awareness [10], especially if combined with proper education [11].

Irrespective of the mode of treatment, there are several well-defined factors influencing hypoglycemia awareness or perception. It was shown that avoidance of exposure to hypoglycemia can restore hypoglycemia awareness [12, 13], even brief and relatively rare episodes of hypoglycemia reduce the detection rate of clinical hypoglycemia in T1DM individuals [14]. Other risk factors for impaired low glucose perception include C-peptide negativity, male gender, and long diabetes duration [15]. Diabetic autonomic neuropathy causes many of the counter-regulatory defects found in patients with hypoglycemia unawareness [16].

Unfortunately, there are very few data concerning factors that may affect hypoglycemia perception among patients treated with personal insulin pumps. Usage of rapid acting analogs during CSII therapy in individuals with hypoglycemia unawareness results in better clinical outcomes in comparison to regular short acting insulin based treatment [17]. However, these data are clinically obsolete, since regular human insulin is hardly ever used in CSII [7, 8, 9]. Other CSII-specific factors that may influence hypoglycemia perception remain to be identified.

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Aim of the study. In this observational study, an attempt was made to asses clinical factors that might affect subjective awareness of hypoglycemia in CSII-treated T1DM patients, with special attention to factors specific for this mode of treatment.

MATERIAL AND METHODS

For the purpose of the study, data of 110 CSII treated T1DM patients were collected (78 females and 32 males). Demographic (gender, age), anthropometric measures (BMI), diabetes-related variables (complications, diabetes duration, insulin pump therapy duration and HbA1C values) were obtained from the patients' clinical files. Patients with advanced microvascular complications of diabetes were excluded from the study. Records were analyzed from glucose meter and insulin pump from the last 3 years. As for glucose meters, during each visit, 200-300 measurements/download were obtained, depending on meter type. These data were used to calculate glycemia statistics and the number of hypoglycemic events (defined as glucose levels below 55 mg/dL or 3.0 mmol/l) per 100 measurements. Insulin pump data were downloaded regularly during each visit via the Carelink Professional or AccuChek Smart Pix software. In the search for factors that could influence hypoglycemia perception, data were analyzed concerning total insulin dose, basal/bolus ratio, number of boluses/day, bolus calculator and dual wave/square bolus usage, and continuous glucose monitoring data. Individuals included into the study completed a questionnaire concerning the level of glucose at which they perceive symptoms of hypoglycemia. On this basis, they were divided into 3 subgroups (1^{st}<50 mg/dl, 2^{nd} (50-70 mg/dl), 3^{rd}(≥70 mg/dl). As for statistical analysis, data were presented as the number of cases, mean or percentage. Normality was tested with the W Shapiro-Wilk test. The correlation 'r' coefficient (R Spearman) was used to analyze the relation between the several variables studied, with significance level of 5% ($p<0.05$). Differences in outcomes were evaluated by using one-way analysis of variance ANOVA or the Kruskal–Wallis test (non-parametric ANOVA). Multivariate linear regression with stepwise selection using a p value of <0.05 as the threshold for adding a variable was used to determine predictors of impaired hypoglycemia perception. All p values are two-sided. All the statistical procedures were performed using the Statistica program for Windows by StatSoft, Inc., version 10.

RESULTS

It was found that the level of subjective hypoglycemia perception inversely correlated with the number of hypoglycemic episodes per 100 measurements ($n = 100$, $r = -0.34$, $p = 0.0006$), age ($n = 110$; $r = -0.26$; $p = 0.0050$), duration of diabetes ($n = 110$; $r = -0.19$; $p = 0.0409$), time on insulin pump ($n = 110$; $r = -0.19$; $p = 0.0447$), and positively correlated with mean glycemia ($n = 98$; $r = 0.22$; $p = 0.0286$). There was no evidence of correlation with HbA1c level ($p = 0.0836$), BMI ($p = 0.9805$), number of blood glucose measurements per day ($p = 0.6501$), daily insulin dose ($p = 0.5514$), insulin units per kg of body weight ($p = 0.7863$) and number of boluses per day ($p = 0.8425$).

With respect to CSII-related factors, hypoglycemia perception inversely correlated with percent of basal insulin ($n = 106$; $r = -0.20$; $p = 0.0354$) (Tab. 1). Usage of pump tools, such as a bolus calculator, dual wave boluses or CGMS, had no impact on hypoglycemia perception (Tab. 2). For the purpose of the multivariate analysis, 8 variables were included in the multivariate model (6 variables for which statistical significance was obtained in the correlation analysis, and *per force* HbA1c and gender). Eight cases, for which the distance of Cook was greater than 2.5, were removed from the analysis. An essential predictive model of hypoglycemia perception was created ($p<0.0000$). The assumptions of the analysis were fulfilled. In stepwise regression analysis, the independent predictors for impaired hypoglycemia perception were: age $\beta = -0.29$ ($p = 0.023$), duration of diabetes $\beta = -0.24$ ($p = 0.029$) and number of the hypoglycemia episodes for 100 measurements $\beta = -0.33$ ($p = 0.0005$). This model, however, enabled only 29% of variation of studied parameter ($R^2 = 29$) to be explained. No other independent variables achieved nominal statistical significance in the multivariate model of impaired hyperglycemia perception.

DISCUSSION

The presented study confirms the findings of previous analyses that hypoglycemia perception may be affected by the frequency of hypoglycemic episodes per 100 measurements, mean glycemia, age, duration of diabetes [12, 13, 14, 15]. Since CSII- treated patients were analyzed, an attempt was also made to identify factors that may influence hypoglycemia perception and are specific for this mode of treatment. An inverse correlation was found between hypoglycemia perception and the percentage of basal insulin in the total daily insulin dose during CSII therapy. However, it was not possible to confirm this finding in the multivariate analysis, perhaps due to the relatively small number of patients in the studied groups. As little as one third of variation of the parameter with multivariate analysis could be explained, which means that hypoglycemia perception is probably multifactorial, and some of the factors affecting it remain to be identified.

It can be speculated that a higher basal insulin dose may lead to more frequent hypoglycemia, and thus impair hypoglycemia perception. Such a correlation between the basal/bolus insulin ratio and the risk of hypoglycemia has been shown previously by Blasetti et al. [18]; however, the

Table 1. Correlation of clinical variables with hypoglycemia perception.

Pairs of variables: hypoglycaemia perception vs.	N	R Spearman	p
HbA1c	107	0.17	0.0836
Age	110	-0.26	0.0050
Duration of diabetes	110	-0.19	0.0409
Time on insulin pump	110	-0.19	0.0447
BMI	107	0.00	0.9805
Mean glycaemia	98	0.22	0.0286
Number of blood glucose measurements per day	98	-0.05	0.6501
Daily insulin dose	105	-0.06	0.5514
Insulin units per kg of body weight	106	-0.02	0.7863
Percent of basal insulin	106	-0.20	0.0354
No. of boluses per day	105	0.02	0.8425
No. of hypoglycemic episodes per 100 measurements	100	-0.34	0.0006

Table 2. Patient characteristics in three groups divided according to level of subjective hypoglycaemia perception (<50 mg/dl, 50-70 mg/dl, ≥70 mg/dl) and results of Anova and post-hoc tests

Variable		<50 mg/dl N = 14	[50-70 mg/dl N = 73	> = 70 mg/dl N = 23	Mean [x_{sr}]	p
HbA1c [%]		6.90	7.27	7.43	7.25	0.3352
Gender	F [n]	11	52	15	-	0.6827
	M [n]	3	21	8		
Age [y]		34.8	26.7	24.2	27.2	0.0140*
BMI [kg/m^2]		24.2	22.9	23.6	23.2	0.0803
Diabetes duration [y]		15.8	13.2	10.1	12.9	0.1224
Time on CSII [y]		4.9	4.5	3.4	4.3	0.1088
Mean glycaemia [mg/dl]		136.8	150.2	155.7	149.7	0.0760
Blood glucose measurements per day [n]		6.9	5.7	6.0	5.9	0.2897
No. of boluses per day [n]		6.2	5.8	6.0	5.9	0.4110
Daily insulin dose [Iu]		46.3	46.6	45.0	46.2	0.6788
Percentage of basal insulin [%]		42.6	40.8	36.5	40.1	0.0819
Insulin unit per kg of weight [Iu/kg]		0.69	0.71	0.69	0.70	0.6939
Hypoglycaemia episodes per 100 measurement [n]		7.6	5.9	3.2	5.5	0.0028**
Dual Wave Bolus/ Square Bolus [n]	Use	2	10	2	-	0.7734
	Do not use	11	61	21		
CGMS [n]	Use	5	15	3	-	0.2052
	Do not use	8	55	20		
Bolus Calculator [n]	Use	7	39	8	-	0.2138
	Do not use	6	31	15		

p values for ANOVA analysis of differences among studied groups.
For post hoc analysis (Scheffe's Test):
* – Group 1 vs. Group 3 (p = 0.0111)
** – Group 3 vs. Group 1 (p = 0.0073) and vs. Group 2 (p = 0.0099)

problem of hypoglycemia perception itself, contrary to the presented analysis, was not addressed. It was shown that the optimal basal/bolus ratio is age-dependent, but for young adult individuals the percentage of basal insulin should be generally around 40% or less [19]. This is also true for older patients with T1DM [20].

CONCLUSION

To summarize, risk factors for impaired hypoglycemia perception in CSII treated patients include those identified previously for the general population of T1DM individuals. As for modifiable CSII-specific factors, the presented results suggest that a higher basal/bolus ratio may lead to impairment of the ability to perceive early symptoms of hypoglycemia.

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