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The phenomenon of HbA1c stability and the risk of hypoglycemia in long-standing type 1 diabetes

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ABSTRACT

Aims: Hyperglycemia is the major factor underlying vascular complications of diabetes. Unfortunately, improved glycemia control is frequently accompanied by an increased risk of hypoglycemia. The aim of the study was to assess the relationship between hemoglobin A1c (HbA1c) and 1-week Continuous Glucose Monitoring (CGM) data in long-standing type 1 diabetes (T1DM).

Methods: We recruited 58 subjects with long-standing T1DM consecutively enrolled to the study. Each patient underwent a 1-week CGM and laboratory profile at baseline. Subjects were divided into three subgroups according to baseline HbA1c tertiles: T1 < 7.1%, T2 = 7.1–8.0%, and T3 > 8.0%.

Results: T1 patients were characterized by the longest time in range (66% of a week), whereas T3 patients experienced hyperglycemia in >50% time of the week. T1 patients were noted to have 25% of nighttime with glycemia <3.9 mmol/L (8% with glycemia <2.8 mmol/L). Most recent HbA1c closely reflected 10-years mean HbA1c values ($R = 0.83$; $P < 0.0001$).

Conclusions: (1) Long-term diabetes control (10 years HbA1c mean) is a strong predictor of the current HbA1c levels. (2) Current and historical HbA1c levels are closely linked to CGM-derived glycemia. (3) Risk of clinically significant hypoglycemia negatively correlates with HbA1c. (4) HbA1c > 8.0% is associated with unsatisfactorily low (44%) time in range.

1. Introduction

Hyperglycemia is the major factor underlying vascular complications of type 1 diabetes [1]. The DCCT trial has undoubtedly demonstrated that intensive treatment (HbA1c average of 7% vs. 9% in the comparison group) reduces both development and progression of microvascular disease in patients with type 1 diabetes [2]. Importantly, long-term follow-up of the DCCT/EDIC cohort has demonstrated that such treatment is also associated with improved cardiovascular outcomes [3–5]. However, the main clinical adverse event related to intensive reduction in HbA1c is a two-to three-fold increase in severe hypoglycemia [1,6].

There is growing evidence that hypoglycemia *per se* might be a cardiovascular risk factor, limiting the benefits of intensive diabetes treatment [7–10]. Earlier studies on the

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prevalence, mechanisms, and consequences of hypoglycemia focused on HbA1c measurements and self-monitoring of blood glucose [11,12], i.e. on methods which remain the gold standard of assessment of diabetes treatment. However, the advent of continuous glucose monitoring (CGM) has shown that patients with comparable HbA1c values may exhibit markedly different patterns of diurnal glucose excursions [13,14]. Consequently, CGM-based studies could provide direct insights into the link between HbA1c, achieved glucose time in range, and prevalence as well as severity of hypoglycemia [15].

Previous studies linking HbA1c to CGM-derived glycemia in type 1 diabetes focused on elderly patients with severe hypoglycemia [16], or analyzed short-term (1–2 days) monitoring results in both hospital [17] as well as outpatient setting [18].

The relationship between HbA1c and hypoglycemia risk as assessed by 1-week use of continuous glucose monitoring in long-standing type 1 patients has not yet been fully elucidated. Furthermore, none of the previous studies assessed this relationship in the context of repeated HbA1c assessment in long standing diabetes. Individuals suffering from type 1 diabetes for more than 20 years are exposed to a particularly high risk of severe hypoglycemia.[19] While general HbA1c target value in type 1 diabetes is <7%, we hypothesized that it may be associated with significant risk of hypoglycemia. Therefore, the aim of the study was to evaluate the relationship between current and historical HbA1c values and hypoglycemia risk as assessed by continuous glucose monitoring in long-standing type 1 diabetes.

2. Subjects

2.1. Study population

Between 2014 and 2016 we recruited 58 subjects with type 1 diabetes among patients of the Outpatient Clinic at the Department of Hypertension and Diabetology, at Teaching Hospital of the Medical University of Gdańsk, Poland. The main inclusion criteria were duration of diabetes of 20 years or longer and willingness to participate in the study. There were no exclusion criteria. At the time of study enrollment, all patients have been treated in our centre for more than 15 years. All subjects were on intensive insulin therapy. Fifty two patients were on basal-bolus regimen using short- and long-acting insulin analogs. Six patients were treated with insulin pumps.

3. Materials and methods

3.1. Study design

Each patient underwent continuous glucose monitoring with the use of *Ipro®2* (*Medtronic MiniMed, Inc.* Northridge, California, USA). Study participants were trained to use the devices in the setting of our Outpatient Clinic. The devices were validated for glycemic range between 2.2 mmol/l and 22.2 mmo/l. CGM recording was performed for seven consecutive days in a regular patient environment and without any changes to treatment regimen or meal plan. Patients were blinded to CGM-device logs (e.g. were unable to see readings) and adjusted insulin injections based on blood glucose meter values. CGM data were considered valid when 80% of scheduled time was recorded. During the CGM recording, each patient was asked to complete a diary providing detailed information regarding meals, treatment, and physical activity. Default target glycemia—as measured with a CGM device—was defined as 3.9–10.0 mmol/l. Hypoglycemia was defined as <3.9 mmo/l, and values <2.8 mmol/l were defined as clinically significant hypoglycemia [20]. Hyperglycemia was defined as glucose levels ≥10.0 mmo/l.

10-Years mean HbA1c was averaged from mean annual calculations (at least 2 measurements each year).

Physical examination including BMI (Body Mass Index), RR (blood pressure), HR (heart rate) and selected laboratory blood tests were performed at baseline. HbA1c was estimated with the use of high performance liquid chromatography (HPLC).

Study protocol was in accordance with the Declaration of Helsinki on the treatment of human subjects and approved by the local ethics committee approved the study (NKBBN/283/2014). Written informed consent was obtained from all subjects.

3.2. Statistical analysis

Data were tabulated in *MS Excel* 2010, and statistical tests were performed with the use of Statistica 12 (*Statsoft Inc.®*, Statistica, Poland) licenced to Medical University of Gdańsk, and Medcalc ver. 17.2 (MedCalc Software bvba, Ostend, Belgium) licenced to JW.

Descriptive variables were presented as means ± SE. The proportion of patients with a given condition was expressed as percentage. ANOVA test was used to compare continuous variables across the 3 subgroups delineated by study baseline glycated hemoglobin tertiles. Tukey-test was used for post-hoc analyses. Chi-squared test (with Yates correction when appropriate) was used to compare co-morbidities. To compare correlation coefficient, Fisher's R to Z transformation was performed. Linear regression model was used to evaluate Pearson-correlation coefficients and scatter plots for several continuous variables. Logistic regression model was used to determine odds for clinically significant night-time hypoglycemia. $P < 0.05$ was considered significant for all calculations.

4. Results

Fifty-six patients (97%) completed the study protocol. Two participants withdrew consent due to personal reasons (none related to medical conditions). Mean duration of CGM recording was 6 days 1 h and 20 min, which accounted for 86.5% of intended seven-day-period. CGM recording was repeated in two patients due to recording duration of less than 80% of scheduled time. In those two cases, mean glycemia as well as glycemia variability was comparable (data not shown). The mean (SD) weekly glycemia of a whole group was 8.7 (2.1) mmol/l and mean HbA1c was 7.9 (1.5) %.

4.1. Relationship between the current and historical HbA1c values

There was a close correlation between the most recent vs. 10-years mean HbA1c values (Fig. 1). Additionally, both study-entrance and historical HbA1c levels correlated with mean CGM-derived glycemia values recorded in different time ranges. However, the relationship was strongest for the day-time glycemia vs. most recent HbA1c P = 0.0505 for the comparison of Z-transformed R-coefficients (Fig. 2).

4.2. Relationship between HbA1c and CGM-based metrics

The patients were divided into three subgroups based on HbA1c tertiles: T1 with HbA1c < 7.1%, T2 with HbA1c 7.1–8.0%, and T3 with HbA1c > 8.0%.

Clinical characteristics of the study group are presented in Table 1. With the exception of HbA1c levels and duration of diabetes, no significant differences in the clinical data between the subgroups were observed (Table 2).

Table 2 summarize the CGM-based metrics in relation to baseline HbA1c tertiles. Patients with HbA1c < 7.1% were characterized by the longest time in range (66% of a week), whereas patients with HbA1c > 8.0% were in hyperglycemic range more than 50% of the monitored time. In patients with HbA1c < 7.1%, 25% of the glucose values were in the hypoglycemic range and 8% of the readings were classified as clinically significant low. In these patients, the prevalence of night-time hypoglycemia was two-fold higher than in the second HbA1c tertile and three-fold higher than in patients with the highest HbA1c values.

4.3. Predictors of night-time clinically significant hypoglycemia.

A multiple regression model adjusted for age, sex, BMI, diabetes duration, HbA1c variation and insulin dose showed that HbA1c of less than 7.1% was the only predictor of night-time hypoglycemia (<2.8 mmol/l) (Fig. 3).

5. Discussion

Firstly, our study demonstrates that HbA1c levels are closely linked to CGM-derived glycemia. This correlation appears to be stronger for day-time than night-time values. Secondly, rate of day-time, and especially night-time, hypoglycemia negatively correlates with HbA1c levels. Thirdly, while HbA1c < 7.1% is associated with high risk of clinically significant night-time glycemia, HbA1c > 8.0% is associated with unacceptably low (44%) time in range. These findings may have important implications for management of patients with long-standing type 1 diabetes.

In our study, the relationship between the current and historical HbA1c levels was strikingly strong. Thus, glycemic control over long period remains in similar range determined by initial HbA1c values. The mechanisms underlying this phenomenon of HbA1c "tracking" are unclear. Whether it might be attributed to "metabolic memory" or rather to constant, despite educational efforts, treatment-related patient behaviour remains to be elucidated by future studies. Identifying factors responsible for this HbA1c stability could help formulate recommendations to improve glucose control in persistently – despite any efforts taken – uncontrolled type 1 diabetes.

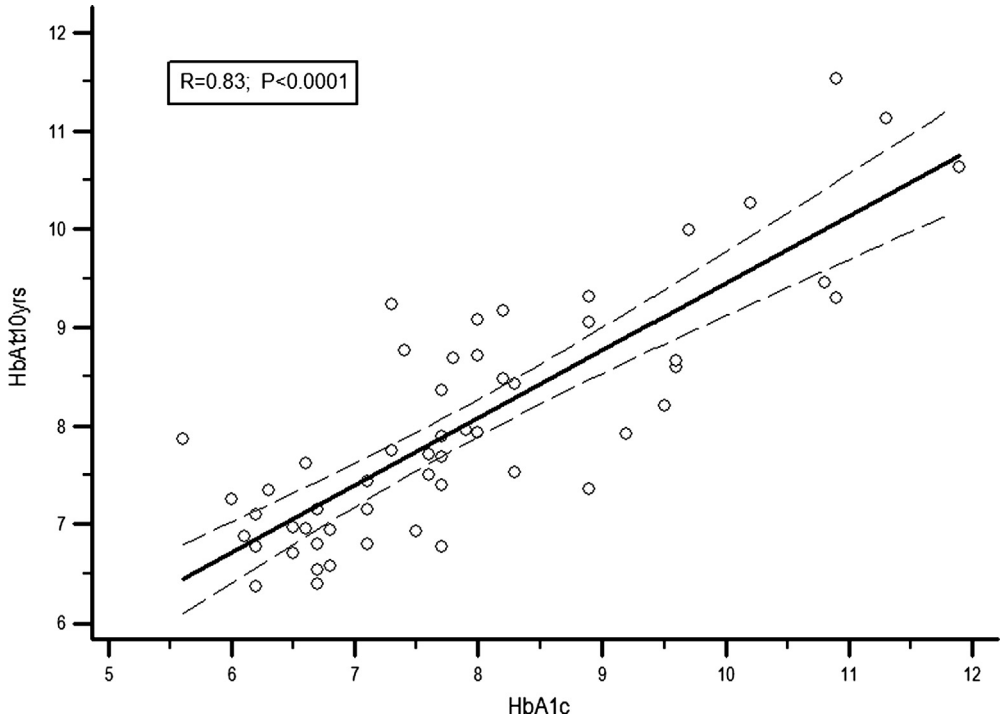

Fig. 1 – Scatter plot of study baseline HbA1c vs. 10-years HbA1c.

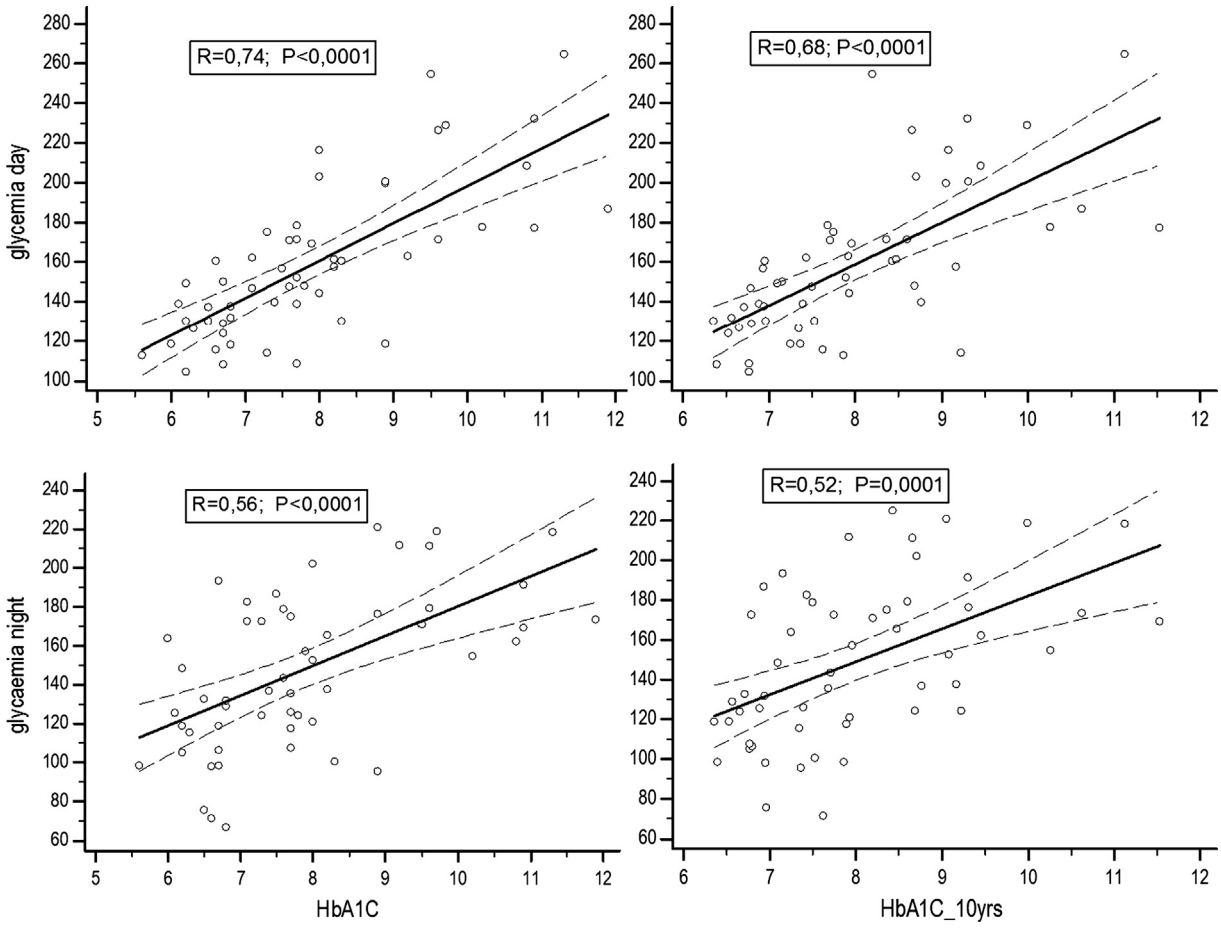

Fig. 2 – Scatter plot of study baseline and historical HbA1c vs. mean day and mean night-time CGM-derived glycemias. HbA1c – study baseline HbA1c assessment; CGM derived mean glycemia extracted from patients' records. Conversion factors to SI units for glucose is as follow: 0.05551.

The assessment of HbA1c level, which accurately reflects the mean glycemic load over the course of the last few months, remains a gold standard to evaluate the quality of diabetes treatment. Consequently, current guidelines on intensity of diabetes treatment, including cardiovascular recommendations, are based on HbA1c. While it may appear reasonable to advocate close-to-normal HbA1c values, the main barrier to achieve strict metabolic control in diabetes is the increased risk of hypoglycemia. It has been recently suggested that appropriate target may be the lowest HbA1c which does not cause severe hypoglycemia and preserves awareness of hypoglycemic symptoms [21]. This statement prompted us to design the present study based on CGM, a method opening a new era in understanding glucose excursions in diabetes, especially with regard to the risk of unrecognized hypoglycemia.

Our study supports the concept that HbA1c levels as an ideal predictor of the diurnal glycemic profile should be taken with caution. Though HbA1c levels closely reflect CGM-derived glycemia, the relationship appears to be stronger for day-time than night-time values (Fig. 2). These findings are not surprising since day-time lasts longer than night-time and thus HbA1c formation is affected by day-time plasma glucose to a greater extent than by a night-time concentration. Therefore, the role of HbA1c in the assessment of the diurnal glycemic profile may be limited during the sleep, however it still bears the potential of identifying patients at risk of unrecognized clinically significant hypoglycemia (Table 2), a condition of particular cardiovascular importance. Nevertheless, our study is consistent with previous data suggesting that a significant proportion of hypoglycemic events cannot be directly attributed to HbA1c levels, as it was also evident in the second and the third HbA1c tertiles (Table 2) [12].

However, the results of previous studies investigating that matter appear to be somewhat conflicting. In the elderly patients with type 1 diabetes, HbA1c and CGM-derived glycemia were comparable in patients with and without severe hypoglycemia [16]. The relationship between HbA1c and CGM results was, however, reported by two other studies [17,18]. In contrast to the latter studies, we assessed one-week CGM data in ambulatory patients with very long (>20 years) duration of disease. Furthermore, we focused on glucose time in range and clinically significant low (<2.8 mmol/l) glycemia, i.e. the two parameters with increasing clinical importance which may become the cornerstone of both monitoring and decision-making in type 1 diabetes.

The most important finding of our study is that patients with HbA1c < 7% were in asymptomatic hypoglycemia for

Table 1 – Baseline characteristics of the study group (n = 56).

Clinical characteristics	Value
Age, y	45.4 (8.7)
Females-to-males (% females)	32:24 (57%)
Duration of diabetes, y	28.9 (7.7)
Insulin regimen:	
Basal, prandial (MDI)	50/56
Insulin pumps (CSII)	6/56
HbA1c, %	7.9 (1.5)
BMI, kg/m^2	25.4 (4.0)
SBP, mm Hg	127.6 (15.5)
DBP, mm Hg	76.6 (8.6)
Diabetic Retinopathy	
No retinopathy	15/56
Non proliferative retinopathy	32/56
Proliferative retinopathy	9/56
Diabetic nephropathy	
Absent	46/56
Microalbuminuria	7/56
Macroalbuminuria	3/56
eGFR (MDRD), ml/min/1.73 m^2	85.6 (9.1)
>90	42/56
60–89	12/56
30–59	2/56
Diabetic symptomatic neuropathy	23/56
Diabetic macroangiopathy	8/56

Data are presented as means (±SD), cases proportion.

Abbreviations: HbA1c, hemoglobin A1c, MDI, multiple dosage of insulin, CSII, continuous subcutaneous insulin infusion, BMI, body mass index, SBP, systolic blood pressure, DBP, diastolic blood pressure, eGFR, estimated glomerular filtration rate, MDRD, Modification of diet in Renal Disease.

approximately one-fourth of their sleep duration. One-third of these events could be classified as clinically significant hypoglycemia (<2.8 mmol/l). In contrast, the prevalence of hypoglycemia was 12% in patients with HbA1 7.1–8.0% and only 7% in patients with HbA1c > 8.0%. However, in the latter group, the time in target range was insufficiently short (44%). Thus, HbA1c 7.1–8.0% appears to be a compromise with both reasonable time in range and acceptable hypoglycemia risk. Due to the phenomenon of stability of HbA1c values we believe that this observation remains valid at any stage of diabetes.

The main limitation of our study is its cross-sectional design. Its strength stems from the homogeneity of the patient group, both in terms of diabetes duration as well treatment method. All of our subjects were on basal-bolus regimen with insulin analogs—according to recommendations of the Polish and international guidelines—for at least ten years prior to the study and only in several cases, pump therapy was introduced in the last few years. Our group represents patients with good long-run metabolic control; the average HbA1c was 7.8% with low prevalence of symptomatic or severe hypoglycemia events. There were only 5 patients with hypoglycaemia unawareness in our group based on previous history. However, during blinded CGM recordings many of daytime, and most nighttime episodes of hypoglycemia were asymptomatic (based on the diaries analyses). As recently shown, such episodes may be associated with relevant cardiovascular control abnormalities including cardiac arrhythmias which confer cardiovascular risk in T1DM patients [29]. In fact, no severe hypoglycemic episodes were observed during a 7-day monitoring. The lower than expected incidence of overt hypoglycemia

Table 2 – Clinical characteristics with relation to baseline HbA1c tertiles and CGM data (6 week).

	HbA1c < 7.1%		HbA1c 7.1–8.0%		HbA1c > 8.0%	
Anthropometrics:						
Age, y	46.8 ± 2.1	(42.6; 50.9)	45.3 ± 2.1	(41; 49.5)	44.3 ± 2.1	(40; 48.5)
Waist, cm	84.8 ± 3.0	(78.7; 90.9)	82.6 ± 3.1	(76.4; 88.9)	86.0 ± 3.1	(79.7; 92.3)
Body weight, kg	73.2 ± 3.6	(66; 80.3)	72.5 ± 3.7	(65.2; 79.9)	77.2 ± 3.7	(69.8; 84.6)
BMI, kg/m^2	25.1 ± 0.9	(23.2; 26.9)	24.6 ± 0.9	(22.7; 26.5)	26.5 ± 0.9	(24.6; 28.4)
Males:females (% females)	10:9	(47.4%)	8:11	(57.9%)	6:12	(66.7%)
Diabetes duration, y	33.4 ± 1.6	(30.1; 36.6)	26.7 ± 1.6	(23.4; 29.9)[a]	26.4 ± 1.7	(23; 29.7)[a]
HbA1c, study baseline	6.4 ± 0.2	(6.1; 6.8)	7.6 ± 0.2	(7.3; 7.9)[a]	9.6 ± 0.2	(9.3; 10)[a,b]
Averaged glycemia values, (mmol/l):						
Mean weekly glycemia	7.0 ± 0.3	6.3; 7.7	8.7 ± 0.4	(7.9; 9.4)	10.4 ± 0.4	(9.6; 11.1)[a]
Minimal weekly glycemia	2.4 ± 0.1	(2.2; 2.6)	2.5 ± 0.1	(2.3; 2.8)	3.0 ± 0.1	(2.8; 3.3)[a,b]
Maximal weekly glycemia	16.7 ± 0.6	(15.4; 17.9)	19. ± 0.6	(17.9; 20.5)[a]	20.6 ± 0.6	(19.3; 21.9)[a]
Fraction of weekly CGM time (target > 0.7)	0.9 ± 0.0	(0.8; 0.9)	0.9 ± 0.0	(0.8; 0.9)	0.9 ± 0.0	(0.8; 0.9)
Cumulative weighted time (%):						
24 h (glycemia 3.9–10.0 mmol/l)	68.1 ± 3.3	(65.1; 74.6)	58.1 ± 3.4	(51.3; 64.8)	44 ± 3.4	(37.2; 50.7)[a,b]
Night-time (glycemia < 3.9 mmol/l)	24.7 ± 3.3	(18.1; 31.3)	11.6 ± 3.4	(4.9; 18.4)[a]	6.9 ± 3.4	(0.2; 13.7)[a]
Day-time (glycemia < 3.9 mmol/l)	12.2 ± 1.4	(9.4; 15.1)	7.9 ± 1.4	(5; 10.8)	4.5 ± 1.4	(1.6; 7.5)[a]
Night-time (glycemia < 2.8 mmol/l)	8 ± 1.8	(4.4; 11.7)	4.6 ± 1.9	(0.8; 8.4)	1.3 ± 1.9	(−2.6; 5.1)[a]
Day-time (glycemia < 2.8 mmol/l)	2.7 ± 0.5	(1.7; 3.6)	1.8 ± 0.5	(0.9; 2.8)	0.7 ± 0.5	(−0.3; 1.7)[a]
24 h (glycemia > 10.0 mmol/l)	16.5 ± 3.7	(9; 24)	33.1 ± 3.8	(25.4; 40.8)[a]	50.9 ± 3.8	(43.2; 58.6)[a,b]
Morning Hrs (glycemia > 10.0 mmol/l)	14.7 ± 4.6	(5.4; 23.9)	30.5 ± 4.7	(21.1; 40)	47.9 ± 4.7	(38.4; 57.3)[a,b]

Data presented as means with standard errors, (95% CI); or cases proportion.

[a] $P < 0.05$ vs. first tertile.

[b] $P < 0.05$ vs. second tertile.

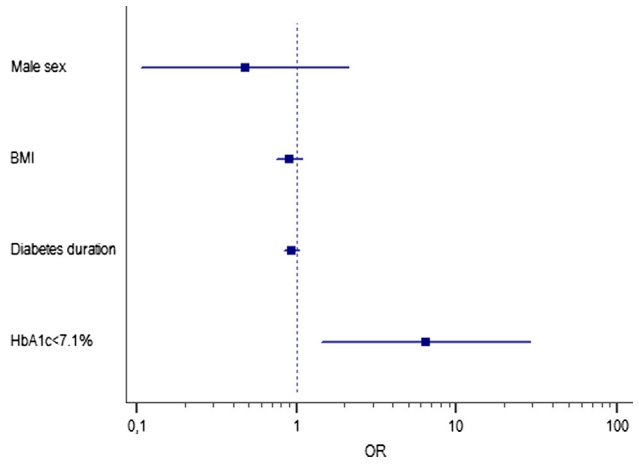

Fig. 3 – Logistic regression analysis. Odds for night-time clinically significant hypoglycemia defined as 3rd tertile of longest cumulative CGM-based glycemia of less than 2.8 mmol/l . CGM data assessed for seven consecutive days between midnight and 0600 a.m. P = 0.04 for the model. Legend: BMI – body mass index [kg/m^2]; HbA1c – as assessed at study baseline. Age and daily insulin/kg (both, as categorical variable with different cut-off points or as continuous variable) were irrelevant.

could be attributed to the fact that the subjects were under care of specialized diabetes centre and participated regularly in diabetes self-care educational programs, which also focus on preventing hypoglycemia.

In summary, the risk and prevalence of unrecognized hypoglycemia is very high in patients with long-standing type 1 diabetes who achieve strict metabolic control with Hb1Ac level < 7%. Hypoglycemia may lead to seizures, injuries and coma, and, if recurring, may contribute to reduced quality of life and cognitive decline [22]. There is also an increasing evidence suggesting a cumulative effect of hypoglycemic events on cardiovascular risk. Patients with higher severe hypoglycemia rate have more advanced coronary artery calcification [23] and higher risk of all-cause mortality and CVD [24,25]. These findings have fuelled the discussion on optimal glycemic target in patients with long-standing type 1 diabetes [26] who are at high risk of developing CVD. Growing recognition of cardiovascular consequences of hypoglycemia is reflected by a tendency to liberalize and individualize target HbA1c values taking into account the individual patient risk profile [27,28]. Our results provide support for current recommendation of highly individualized treatment goals since strict metabolic control in long-standing diabetes is clearly associated with unacceptably high incidence of hypoglycemia. Thus, careful assessment of risk-benefit ratio between avoiding excessive hyperglycemia and unrecognized hypoglycemia in this group of patients cannot be overestimated.

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