

**The interrelationship of  
HbA1c and real-time  
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Tamás Ferenci, Anna Körner, Levente  
Kovács

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## Title page

Title: The interrelationship of HbA1c and real-time continuous glucose monitoring in children with type 1 diabetes

Authors' names: Tamás Ferenci<sup>a</sup>, Anna Körner<sup>b</sup>, Levente Kovács<sup>a</sup>

Authors' affiliations: a: Óbuda University, John von Neumann Faculty of Informatics, Physiological Controls Group, Budapest, Hungary, H-1034

Bécsi út 96/b b: Semmelweis University, 1<sup>st</sup> Department of Paediatrics, Budapest, Hungary, H-1083 Bókay János u. 53-54.

Authors' email addresses: Tamás Ferenci: ferenci.tamas@nik.uni-obuda.hu,

Anna Körner: korner.anna@med.semmelweis-univ.hu, Levente Kovács:

kovacs.levente@nik.uni-obuda.hu.

Corresponding author: name: Levente Kovács, address: H-1034 Budapest,

Bécsi út 96/b, telephone number: 36 (1) 666-5585, fax number: 36 (1) 666-

5522, e-mail address: kovacs.levente@nik.uni-obuda.hu.

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## **Abstract**

**Aims:** The aim of this observational study is to investigate the relationship between age, duration of diabetes, HbA1c and the parameters of glucose levels measured with real-time CGM in children with type 1 diabetes.

**Methods:** Glucose level was characterized with the relative time spent in hyper- and hypoglycemia, central tendency, variability and MAGE during (real-time) CGM. These parameters were measured in 57 children with type 1 diabetes mellitus. The univariate association of the measured parameters was investigated with scatterplots as well as with linear and distance correlation coefficients.

**Results:** Age and duration of diabetes was not clinically relevantly associated with any descriptor of glucose level. HbA1c had an overall positive association with variability and MAGE observed during CGM. Slight, but non-significant, positive association of HbA1c was observed with the time spent in hyperglycemia and the central tendency of glucose level. With the exception of MAGE, the associations of the descriptors with HbA1c are non-monotonic, with a temporary break in the positive correlation at 10%.

**Conclusions:** The results confirmed the well-known positive association of HbA1c with the central tendency of glucose level. The non-monotonic relationship between HbA1c and the indicators of the central tendency of

glucose level might be caused by the varying adherence of the patients during the CGM registration. HbA1c's positive association with MAGE without that non-monotonicity underlines MAGE's usefulness in the reliable assessment of the patients' glycemic state.

## **Keywords**

Pediatric type 1 diabetes mellitus; continuous glucose monitoring; glucose variability; Hawthorne effect; HbA1c.

# 1. Introduction

Type 1 diabetes is one of the most common chronic disorders in children and adolescents. Several factors play a role in the pathogenesis of the complications in diabetes. Improved metabolic control in particular might prevent or postpone late vascular complications, as has been demonstrated by many studies, mainly by the Diabetes Control and Complications Trial [1] as well as by Epidemiology of Diabetes Interventions and Complications [2]. Glycemic control is usually determined by measurement of glycated hemoglobin (HbA1c). However, patients with similar glycated hemoglobin levels and mean glucose values can experience different glycemic fluctuations. Evidence implicates glycemic variability, mostly present in the form of postprandial glycemic spikes, as a key factor in the development of the complications of diabetes [3].

New technological improvements, especially continuous glucose monitoring (CGM) technique, which consists of a disposable transcutaneous glucose sensor along with an electronic transmitter/receiver unit [4], allows a more precise follow-up of the glucose evolution in vivo. Monitoring might be blinded to the patient which is used to inform healthcare professionals about the patient's glucose evolution, or non-blinded, also called personal or real-time CGM (RT-CGM), where the receiver is supplemented with a graphical display which allows the patients to have a direct, almost minute-to-minute

observation of their own glucose level, thus enabling a better management of their diabetes. This has demonstrated to improve glucose control [5-6].

By their 5 minutes measurement frequency (288 measurements per day) the possibilities of CGM have direct effect on short term monitoring, but questions are raised on its usefulness for evaluating long-term outcome. The most important classical indicator in this sense is HbA1c that reflects the average glucose level of a patient over 120 days (the “life cycle” of red blood cells) [7]. Beside HbA1c, glycemic variability is now suggested to play role in the appearance of long-term complications of diabetes [8-9].

Correlation of HbA1c and glucose itself is well known, but CGM opened new horizons in a more thorough investigation of this issue [10-12]. The aim of the current work is to evaluate the relationship between age, duration of diabetes and HbA1c on the one hand, and glycemia measured with CGM on the other hand in children with type 1 diabetes.

## **2. Material and methods**

### **2.1. Study population and design**

Fifty seven children with type 1 diabetes mellitus (DM) were selected as a convenience sample from the database of the 1<sup>st</sup> Department of Paediatrics of Semmelweis University (Budapest, Hungary), with CGM measurement data between July 2009 and February 2011. Only patients with at least 1 year of DM duration were included so that even HbA1c had time to reach its characteristic levels.

The vast majority of the patient were poorly controlled (according to the guidelines [13] of the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes [14-16]) with CGM performed to optimize therapy. CGM measurements were non-blinded to the patients, i.e. real time (RT)-CGM was employed.

The sample included patients using continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) treatment regimes. The CGM sensors were accurate and reliable, time to sensor failure, frequency and duration of data gaps were negligible, the alarms worked properly. Sex, age, duration of diabetes and HbA1c at the time of the CGM measurement were extracted for each patient from the electronic records of the hospital

information system. HbA1c was measured with NGSP certified method.

The summary of these patient characteristics is shown in Table 1.

CGM recordings were electronically processed (by exporting them to comma separated values format using the software of the device manufacturer) and the following parameters were extracted from the time series of glucose measurements to characterize the clinically relevant aspects of the patients' glucose evolution:

- Time spent in hyperglycemia and hypoglycemia relative to the whole length of recording (hypoglycemia was defined as glucose level  $< 3.9$  mmol/l, hyperglycemia was defined as glucose level  $> 10$  mmol/l) in [%].
- Central tendency of glucose levels (quantified with mean and median glucose level) in [mmol/l].
- Dispersion, i.e. variability of glucose levels (quantified with standard deviation and interquartile range of glucose level) in [mmol/l].
- Glycemic variability as measured by Mean Amplitude of Glycemic Excursions (MAGE), calculated according to the algorithm of Baghurst [17-18]. While there are many glycemic variability metrics described in the literature [19], MAGE was now chosen due to its very widespread use even in spite of its limitations [20], i.e. to show

a representative example of glycemic variability metrics to illustrate their application. Comparison of these metrics is extensively covered in the literature [21].

Summary of these parameters is presented in Table 2.

## **2.2. Statistical analysis**

A pairwise analysis was performed between every possible variable (altogether  $3 \cdot 7 = 21$  pairs). As every variable was quantitative, this was essentially a question of correlation, which was investigated with graphical (scatter plot) and analytical (calculation of correlation coefficients) methods.

Scatter plots sometimes revealed not simply non-linear, but markedly non-monotonic relationships, so the calculation of the linear correlation coefficients is not sufficient. Spearman- $\rho$  correlation coefficient is often applied in situations where non-linearity is encountered [22], however it also falls short in detecting non-monotonic connections. Therefore, a method is needed that characterizes the *overall* dependence of two variables; now a modern metric for this purpose, called distance correlation [23-25] was used. Distance correlation is based on the difference between the joint probability density function of the variables and the product of their marginal density functions (as these should be equal if the variables are independent, hence, their difference characterizes the dependence of the variables). This way, distance correlation does not depend on the nature of

the relationship, it can detect the strength of linear and non-linear, monotonic and non-monotonic, i.e. arbitrary connection between the variables.

Also to facilitate the detection of more complex connections, LOWESS-estimators [26] for the non-parametric regression between the investigated variables were plotted on the scatter plots. Second-degree polynomial were used with a smoothing parameter of 0.75. Ninety-five percent confidence intervals for the regression are also shown. These non-parametric regressions – and their confidence intervals – help visualizing the relationship between the investigated variables (without confining ourselves to any pre-specified function form of the relationship).

Due to the relatively low sample size, we did not attempt to perform an age-stratified analysis, to maintain the reliability of the results.

Statistical analysis and visualization was performed under the R statistical environment, version 3.0.2 [27]. The R script developed for this purpose is available at the corresponding author on request.

### 3. Results

Age and duration of DM showed no clear relationship with any descriptor of the glucose levels as evidenced by the correlation coefficients (Table 3) and the scatterplots (figures not shown here).

HbA1c (Figure 1) however shows a clear – but statistically non-significant – overall positive association with ratio of time spent in hyperglycemia (but not with hypoglycemia). Note that a small, seemingly paradoxical non-monotonic region at about HbA1c=10% can be observed. As far as the central tendency is concerned, again a clear, but statistically non-significant overall positive association can be observed both for mean and median. The paradoxical non-monotonic region around 10% shows up again. However, for glycemic variability, there is a clear and statistically significant positive association (both for standard deviation and interquartile range). The trend change about 10% is not as pronounced as before; rather, a flat region can be seen on the scatter plots.

MAGE (Figure 2) only has a slight positive association with HbA1c (and the paradoxical region around 10% is missing, too).

Linear correlation coefficients are significant for glucose variability vs. HbA1c ( $p < 0.005$ ) and MAGE vs. HbA1c ( $p = 0.0385$ ). Time spent in hyperglycemia is at the border of significance. Distance correlations are significant likewise for variabilities ( $p = 0.0165$  and  $p = 0.0063$ ), and is at the

border of significance for MAGE ( $p=0.0676$ ). Note that distance correlation is always between 0 and 1, as there is no point in talking about the direction of the relationship for a non-monotonic function. The  $p$ -values of the distance correlations are expected to be higher, given the fact that this test has lower power (due to its more general nature).

## 4. Discussion

Duration of diabetes and age is not associated with any indicator of glucose evolution during CGM in clinically relevant way. On the other hand, HbA1c is positively – and statistically significantly – associated with the indicators of the variability of glucose levels and MAGE. Compared to the duration of diabetes and age, stronger and clinically relevant, but statistically still non-significant, overall positive association can be observed between HbA1c and the indicators of the central tendency of glucose level and time spent in hyperglycemia. (Non-significance of these is likely attributable to the low sample size.) These associations – especially for the time spent in hyperglycemia and the central tendency of glucose levels – are not linear, furthermore not even monotonic, as they show a marked temporary decrease around HbA1c=10%.

Note that as now 21 hypothesis testings were performed in parallel (one for each patient characteristic/CGM-property combination), results cannot be compared to the traditional threshold of 5% due to the multiple comparisons situation [28]. However, significant correlations – especially for variability – had magnitude smaller  $p$ -values, so labeling of these as significant association is justified, even in the light of the multiple comparisons situation.

The positive association between the indicators of the central tendency of glucose and HbA1c is well known, even quantitatively [29-31].

Positive association between the indicators of the variability and HbA1c are also described in the literature [32] but not with uniform results [33-34].

Our results also confirm the suggested [34] association between hyperglycemia and HbA1c.

The explanation for the seemingly paradoxical behavior of the association of HbA1c with the various descriptors of glucose levels is possibly the poor adherence that is characteristic for most of the investigated children. The motivation to “cheat” during the CGM-measurements (i.e. to pay closer attention to glucose levels than it is usually done by the children) is higher for those having worse metabolic state (as evidenced by HbA1c higher than 8%). Also, there is not only a motivation, but also a possibility for this, given that the measurements were non-blinded for the children. Hence, it may be hypothesized that children above 8% HbA1c start to increasingly pay unusual – i.e. that is not done without CGM – attention to their glucose levels during CGM measurement, breaking the association between HbA1c and the mean (or median) glucose during CGM. They could, however, do it only up to a point (about 10%) as even worse metabolic states could not be “compensated” by such temporarily increased adherence. This can be more directly illustrated when HbA1c is converted to (long-term) estimated

average glucose and is contrasted with the average glucose (i.e. short-term average) that can be calculated from the CGM recording (Figure 3). The conversion of HbA1c to estimated average glucose was done using the formula  $eAG_{mmol/l} = 1.59 \times HbA1c\% - 2.59$  [29].

This phenomenon is the well-known Hawthorne effect studied in many fields of science, and already described in relationship to CGM as well [35]. Hawthorne effect claims that patients – not necessarily deliberately – alter their behavior when they know that they are under observation.

The small sample size and the convenience sampling of the present study limits the robustness of this conclusion, and further studies are needed to confirm this finding, and – if confirmed – investigate its determinants.

## 5. Conclusion

The results confirmed the well-known positive association of HbA1c with the indicators of the central tendency of glucose (mean, median). No association was found between the duration of the diabetes and the age of the patient with any indicator of the glucose levels.

The relationship between HbA1c and the indicators of the central tendency of glucose are non-monotonic, which is likely caused by the varying adherence of the patients. HbA1c was also positively associated with MAGE, but the non-monotonic region was missing, underlining MAGE's usefulness in the reliable assessment of the patients' glycemic state.

## **6. Acknowledgments**

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## **Author disclosure statement**

The authors declare that they have no conflict of interest.

## **Authors' contribution**

TF performed the statistical analysis and drafted the manuscript. AK conceived the research and provided support in clinical interpretations. LK supervised the project and revised the manuscript. All authors have read and approved the final article.

## **Role of the funding source**

No specific funding was used, neither to conduct the research nor to prepare the article.

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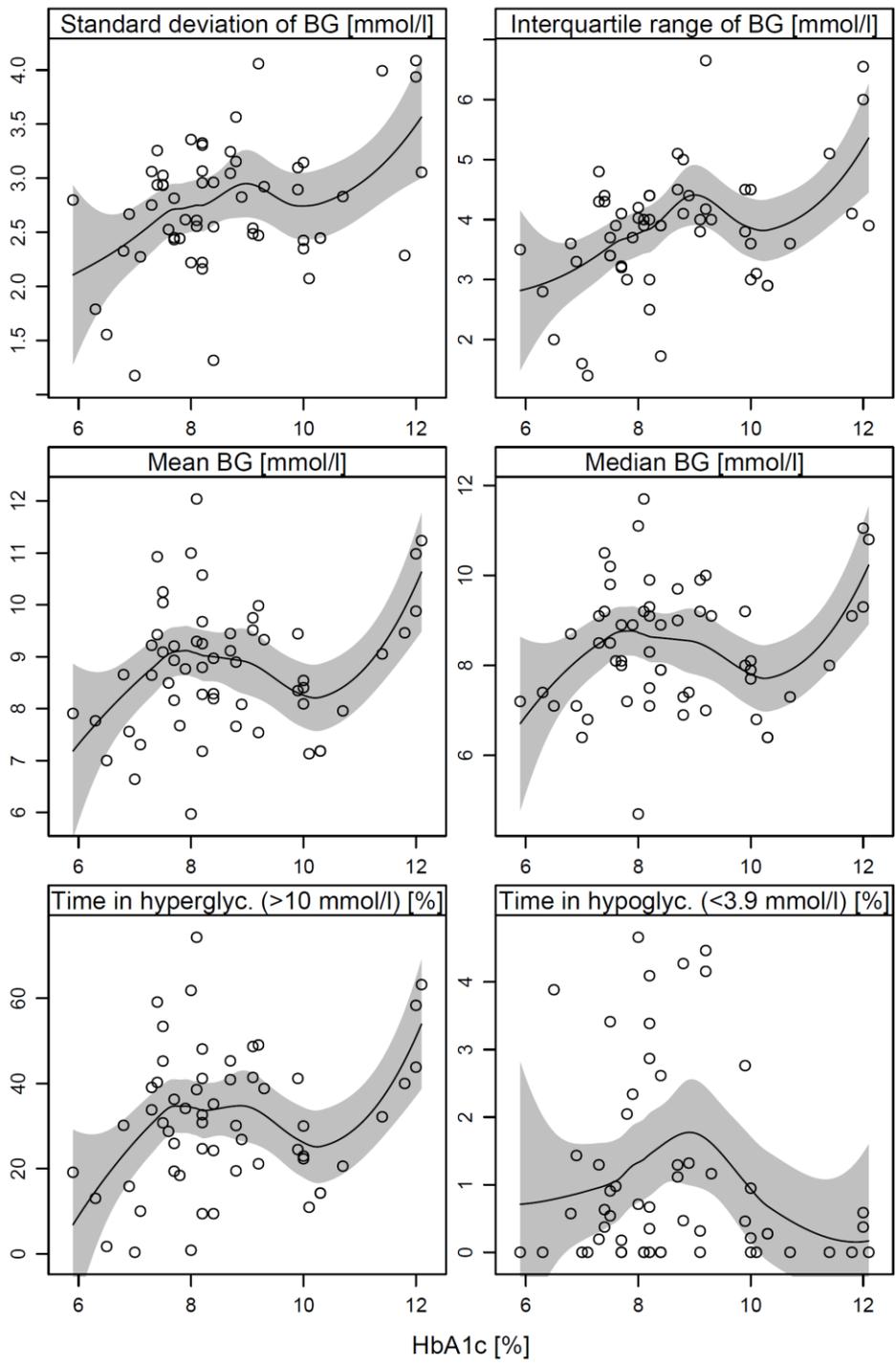
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## Figure captions

### ***Figure 1***

Title: Association of hyper- and hypoglycemia, central tendency and dispersion during CGM with HbA1c.

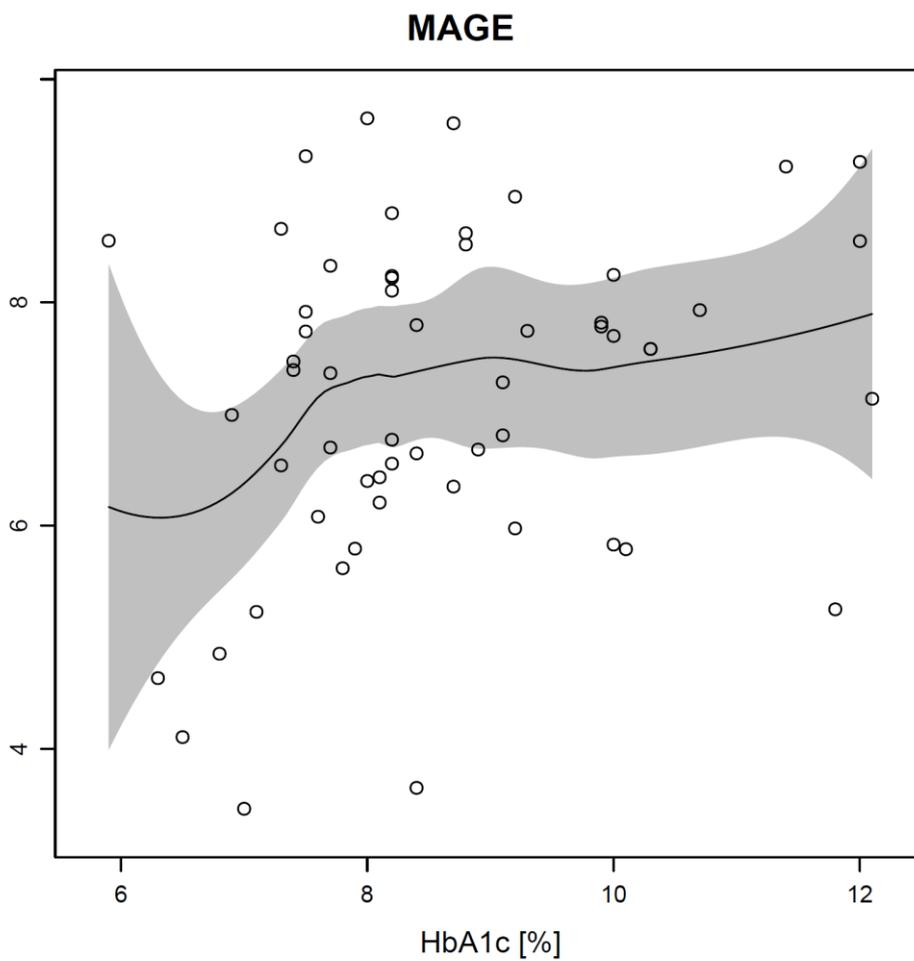
Description: Scatterplots of HbA1c and the various descriptors of the CGM-measured glucose profile. Solid line indicates the best fitting non-parametric regression curve obtained with LOWESS, gray shading shows 95% confidence interval for this curve.



## Figure 2

Title: Association of MAGE during CGM with HbA1c.

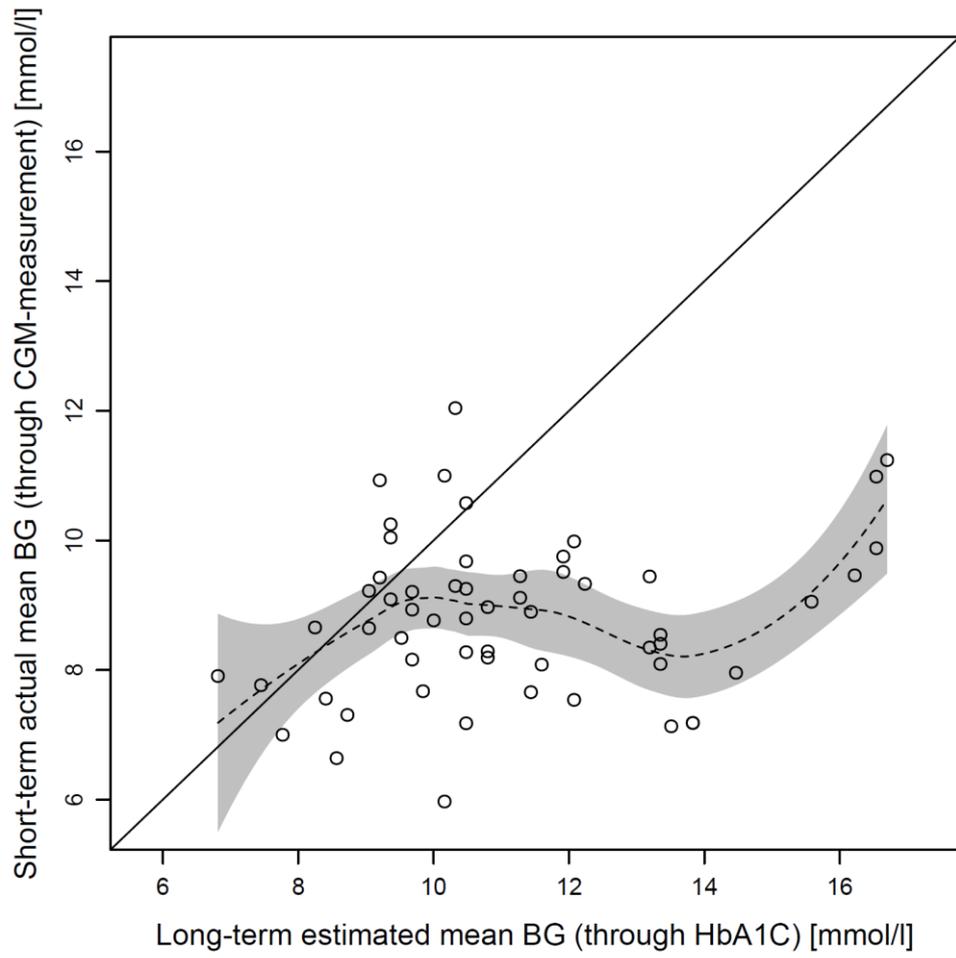
Description: Scatterplot of HbA1c and MAGE of the CGM-measured glucose profile. Solid line indicates the best fitting non-parametric regression curve obtained with LOWESS, gray shading shows 95% confidence interval for this curve.



### **Figure 3**

Title: Estimated average glucose calculated from HbA1c (i.e. long-term average) vs. average glucose during CGM (i.e. short-term average).

Description: Scatterplot of estimated average glucose calculated from HbA1c and average glucose during CGM. Dashed line indicates the best fitting non-parametric regression curve obtained with LOWESS, gray shading shows 95% confidence interval for this curve. Solid line is the reference curve indicating the equality of the two types of average glucose values.



## Tables

**Table 1**

Title: Most important descriptive statistics of the patients' characteristics.

Description: Patient characteristics in *Mean (Median) ± SD (IQR) [Min-Max]* format for continuous variables and as frequency tables for discrete variables.

Parameter	Descriptive statistics
Total number of patients	57
Treatment regime	30 (52.6%) MDI, 27 (47.4%) insulin pump
Length of CGM measurement [hours]	216.9 (161.6) ± 166.7 (258.1) [19.5 – 705.5]
Type of device	47 (82.5%) Guardian REAL-Time 9 (15.8%) Paradigm 522 and 722 1 (1.8%) Paradigm Veo-554
Sex	36 (63.2%) female, 21 (36.8%) male
Age [year]	12.5 (13.0) ± 3.5 (6.0) [4 – 18]
Duration of DM [year]	5.1 (4.0) ± 3.5 (6.0) [1 – 18]
HbA1c [%]	8.6 (8.2) ± 1.5 (1.7) [5.9 – 12.1]
HbA1c [mmol/mol]	70.8 (66.1) ± 16.1 (18.6) [41.0 – 108]

## **Table 2**

Title: Most important descriptive statistics of the investigated CGM parameters.

Description: Descriptive statistics of the indicators derived from CGM-measured glucose evolution in *Mean (Median) ± SD (IQR) [Min-Max]* format.

<b>Parameter</b>	<b>Descriptive statistics</b>
Percentage of time spent in hyperglycemia (>10 mmol/l) [%]	31.3 (30.8) ± 16.3 (21.7) [0.4-74.3]
Percentage of time spent in hypoglycemia (<3.9 mmol/l) [%]	1.1 (0.5) ± 1.4 (1.3) [0-4.7]
Mean glucose level [mmol/l]	8.8 (8.8) ± 1.23 (1.49) [5.97-12.04]
Median glucose level [mmol/l]	8.42 (8.3) ± 1.38 (1.9) [4.7-11.7]
Glucose level standard dev. [mmol/l]	2.75 (2.8) ± 0.59 (0.62) [1.18-4.09]
Glucose level IQR [mmol/l]	3.85 (3.9) ± 1.01 (1.1) [1.4-6.65]
MAGE	7.17 (7.39) ± 1.47 (1.89) [3.46-9.65]

**Table 3**

Title: Correlation of the investigated parameters.

Description: Asymmetric correlation matrix of the investigated parameters (linear and distance correlation coefficients with significance).

		<i>Linear correlation</i>			<i>Distance correlation</i>		
		<b>Age [year]</b>	<b>DM duration [year]</b>	<b>HbA1c [%]</b>	<b>Age [year]</b>	<b>DM duration [year]</b>	<b>HbA1c [%]</b>
<b>Ratio of hyperglycemia (&gt;10 mmol/l) [%]</b>	<i>r</i>	0.04	-0.01	0.24	0.21	0.18	0.27
	<i>p</i>	0.7403	0.9514	0.0775	0.5540	0.7953	0.1642
<b>Ratio of hypoglycemia (&lt;3.9 mmol/l) [%]</b>	<i>r</i>	-0.04	0.02	-0.14	0.15	0.18	0.24
	<i>p</i>	0.7801	0.8723	0.2871	0.8881	0.5777	0.1929
<b>Mean glucose level [mmol/l]</b>	<i>r</i>	0.05	0.03	0.21	0.22	0.20	0.26
	<i>p</i>	0.7226	0.8291	0.1200	0.4637	0.6394	0.1904
<b>Median glucose level [mmol/l]</b>	<i>r</i>	0.02	0.04	0.14	0.20	0.20	0.23
	<i>p</i>	0.8567	0.7689	0.2855	0.6163	0.5904	0.3482
<b>Glucose level standard deviation [mmol/l]</b>	<i>r</i>	0.13	-0.15	0.38	0.22	0.22	0.36
	<i>p</i>	0.3467	0.2730	0.0032	0.4869	0.4757	0.0165
<b>Glucose level IQR [mmol/l]</b>	<i>r</i>	0.09	-0.08	0.42	0.17	0.22	0.39
	<i>p</i>	0.4881	0.5497	0.0013	0.9606	0.5756	0.0063
<b>MAGE</b>	<i>r</i>	0.10	-0.17	0.27	0.19	0.25	0.30
	<i>p</i>	0.4727	0.1989	0.0385	0.7057	0.2390	0.0676

