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Review Article

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OUTCOMES AND EFFECTS ON GLYCEMIC VARIABLITY OF THE USING THE BLIND TYPE OF CONTINUOUS GLUCOSE MONITORING DEVICE IN PEDIATRIC PATIENTS ON MULTIPLE DAILY INSULIN INJECTIONS

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ABSTRACT

Introduction/aim. Through retroactive analysis and statistical processing of the data obtained in the original research conducted in 2016, we want to establish which of the modern parameters of good metabolic control (Time In Range -TIR, Coefficient of Variation – CV and Area Under the Curve below limit - AUC) had the greatest influence on glycated hemoglobin A1c - HbA1c, and whether it is in accordance with modern diagnostic recommendations for the treatment of type 1 diabetes mellitus in the pediatric population. The subjects in the original research were using a professional type of device for continuous monitoring, a blind type of device, and did not have immediate real-time insight into the glycemic values measured by the same, so they could not affect the results obtained. **Methods.** 24 children with type 1 diabetes mellitus (10 boys and 14 girls), aged 5 to 18 years old (average 12.0 ± 3.3), with an average duration of diabetes of 2.5 years, participated in the study. All subjects were treated with multiple daily insulin injections – MDI. According to the study protocol, the subjects were expected to perform control laboratory tests (HbA1c) and certain anthropometric measurements (height, weight, Body Mass Index - BMI) before the beginning of the examination. Each subject had to use a device for professional glucose monitoring once a month for seven days, three times over a three-month period. After each use of the device, the results were discussed with the subject, and if necessary, insulin doses were changed and advice was given on proper nutrition. After three months, HbA1c was again measured in the laboratory. **Statistical analysis.** Initial HbA1c was 7.78±1.17 (min.: 5.5%; max.: 10%). During the period of using the professional device for continuous glucose monitoring, there was a decrease in laboratory-measured HbA1c, and after three months the laboratory-measured average value was 7.34±0.84 (min.: 5.60%; max.: 8.90%). The highest correlation coefficient and the only one that shows statistical significance in connection with laboratory measured HbA1c after three months is the time spent in the target range or TIR, and this correlation is negative. A linear regression model of the dependence of HbA1c on variables (TIR, CV, AUC below) was set up. The obtained R value of 0.820 (R^2=0.673) tells us that the regression of HbA1c 67.3% is influenced by these three variables, the statistically significant of which is TIR (t=-5.411, p≤0.01). **Conclusion.** Subsequent statistical processing of the results showed that the decrease of HbA1c in the original research was most influenced by TIR, which coincides with modern methods and diagnostic recommendations. CV, as well as AUC did not show a direct impact on HbA1c, but did show an impact on TIR, which can be explained by the imperfections of the research itself. Through statistical analysis in this paper, we have shown that all parameters are related and that one depends on the other, so a TIR of 70% does not mean that there is no variability or hypoglycemic episodes, and therefore clinicians must observe all the data obtained using CGM devices in order to determine a good therapy.

INTRODUCTION

The treatment of type 1 diabetes mellitus has advanced rapidly in recent years, combining modern formulations of insulin preparations and medical devices, which patients use more and more often. Insulin pumps are getting to the point where they have perfected insulin delivery methods to completely mimic natural secretion. Continuous glucose monitoring devices are following their lead, but still have a few more minor but significant issues to solve. For now, the best therapeutic effects are achieved by combining them.[1] This technological progress mostly affects the youngest patients group, that is children and adolescents.[2] Furthermore, this technological progress influenced not only the improvement of metabolic control in this group of patients,[3,4] but also changed the diagnostic classification of the disease itself and the parameters that describe good metabolic control. Sadly, data shows that a large number of patients in the world lack these medical tools in order to achieve optimal values of new parameters which show good metabolic control. In America, only 5-23% of patients used CGM devices in

2015, depending on age group.[5] Barriers to using this device in these patients are mostly financial related, as these devices are expensive and not every insurance is willing to cover the cost.[6] New parameters describing good metabolic control are a direct product of the use of continuous glucose monitoring devices, and therefore the use of these devices has been expanding in recent years.

One of the most significant characteristic of the youngest population group of patients is that it is extremely difficult to assess when is the optimal time to introduce CGM into therapy,[7] but it has been shown that adherence and acceptance of the device itself significantly influence the improvement of glycemic regulation, especially if they are introduced as early as possible in therapy. The large amount of data obtained by continuous glucose monitoring devices can confuse both patients and clinicians if they are superficially and incorrectly interpreted. Therefore, the 2017 ATTD consensus describes and explains in detail what values of certain parameters are considered as good metabolic control.[8] Old parameters, which have been used since the DCCT study,[9] such as HbA1c, although still very present in daily clinical practice, due to the lack of CGM devices, are gradually being replaced by TIR (Time In Range), i.e. the time spent in the target range of glucose concentration. Values from 3.9 mmol/L (70 mg/dL) to 10.0 mmol/L (180 mg/dL) were taken as the limits of the range.[10] Many authors examined the relationship between HbA1c and TIR.[11] and all came to the conclusion that lower HbA1c means better TIR. The cut-off value was 70% TIR, which is approximately equivalent to 7.0% HbA1c. In addition to TIR itself, a new parameter that describes good metabolic control is the coefficient of variation (CV). By convention, CV should be less than 36% for good metabolic control in the pediatric population.[11]

The clinical and practical usefulness of these devices in therapy has been proven in a numerous studies in which the improvement of metabolic control during the period of using the CGM devices was demonstrated, and this improvment was reflected in the reduction of HbA1c, as well as hypoglycemic episodes.[12] Although most of these studies were conducted with participants using subcutaneous continuous insulin infusion through an insulin pump, there are also studies with people using multiple daily insulin injections, or MDIs, that came to the same conclusions.[13] Comparing these two groups of patients, with or without an insulin pump, it was shown that in patients without an insulin pump, a significantly greater decrease in HbA1c, i.e. an improvement in metabolic control, is achieved with the use of CGM.[14]

The original research conducted in 2016 showed that there was a statistically significant decrease in HbA1c in children on MDI who used the device for continuous glucose monitoring for the first time.[15] Through retroactive analysis and statistical processing of the data obtained in this research, we want to establish which of the modern parameters of good metabolic control had the greatest influence on this decrease and whether it is in accordance with modern diagnostic recommendations for the treatment of type 1 diabetes mellitus in the pediatric population. It is important to note that all subjects in the original research were using a professional type of device for continuous monitoring, a blind type of device, and did not have immediate real-time insight into the glycemic values measured by the same, so they could not affect on the results obtained.

METHODS

24 children with type 1 diabetes mellitus (10 boys and 14 girls), aged 5 to 18 years (average 12.0 ± 3.3), with an average duration of diabetes of 2.5 years, participated in the study. Criteria for inclusion in the study is a minimum duration of diabetes of one year. All subjects were treated with multiple daily insulin injections - MDI, or bolus-basal type of insulin therapy. (The demographic characteristics of the group are described in Table 1.).

The study protocol was presented to the subjects and their parents/guardians before the start of the study. According to the protocol, the subjects were expected to perform control laboratory tests (HbA1c) and certain anthropometric measurements (height, weight, BMI) before the beginning of the examination. Each subject had to use a device for professional glucose monitoring once a month for seven days, three times over a three-month period. After each use of the device, the results were discussed with the subject, and if necessary, insulin doses were changed and advice was given on proper nutrition. After three months, HbA1c was again measured in the laboratory.

TIR limits are set from 3.9 mmol/L to 10.0 mmol/L, according to recommendations,[8,10] CV was calculated using a mathematical formula for each subject individually, and the obtained values were further entered into the statistical analysis. The calculation formula represents the ratio of the standard deviation of all sensor measurements and the mean value of the glucose concentration measured by the sensor, expressed as a percentage.[12] As a parameter describing hypoglycemic episodes, the AUC below the limit was taken, and it represents the relationship between the duration of an individual hypoglycemic episode and all glucose concentration values measured by the sensor during the duration of the hypoglycemic episode.

Considering that each subject used CGM for longer than 14 days in a period of three months and thus fulfilled the conditions for the calculation of the examined parameters,[8] this essentially represents only 20.72% of the time spent using this device, and that is the first imperfection of this research. The second is a small sample, determined by the characteristics of the population on which the research was conducted.

All examined parameters in the statistical analysis were taken as mean values of all three measurements. This weighted mean value was subsequently obtained by a mathematical formula that used as a weight the minutes spent under CGM at each measurement. Descriptive statistics methods, correlation factors between parameters were used in the statistical analysis, and a linear regression model was set, where the dependent variable was HbA1c after three months of study, and the independent variables were: TIR, CV and AUC below the limit. All variables significant for statistical processing are numerical.

Other variables such as MAGE or LAGE, which show glycemic variation, are not part of this article, as the author wants to examine only the most commonly used variables and their relationship with HbA1c in this article.

Table 1: Demographic caracteristic of the group.

Variable	Value
Average age	12.0±3.3
Time since diagnosis	2.5 (min.: 1; max.: 14)
Average height (cm)	153.83±18.28
Average weight (kg)	45.97±14.88
BMI (kg/m2)	18.80±0.25
Average dose of insulin per kg of body weight (IU/kg)	0.64±0.25
HbA1c at the beginning of the study – laboratory measured (%)	7.78±1.17
HbA1c after 3 months – laboratory measured (%)	7.34±0.84

Values are presented as mean ± standard deviation, except for time since diagnosis, which is presented as median with maximum and minimum values.

Statistical analysis

Initial HbA1c was 7.78±1.17 (min.: 5.5%; max.: 10%). During the period of using the professional device for continuous glucose monitoring, there was a decrease in laboratory-measured HbA1c, and after three months the laboratory-measured average value was 7.34±0.84 (min.: 5.60%; max.: 8.90%). As it shown in original research, this decrease is statistically significant, and the parametars describing that are ΔM=0.45, t=2.67, and P_{bonf} =0.041.[14]

Statistical analysis presented in this article sought to determine which of the parameters of good glycemic control including: time spent in the target range (3.9 mmol/L to 10.0 mmol/L), coefficient of variation (≤36% was taken as a parameter of good metabolic control).[15] and AUC below the limit of 3.9 mmol/L (which should be as close as possible to 0), had the greatest impact on this decrease. Table 2 lists the basic parameters of descriptive statistics for all three variables.

Table 2: Parameters of descriptive statistics for all three variables.

	TIR	CV	AUC (below 3.9 mmol/L)
Mean value	53.64	40.17	0.04
Standard deviation	15.81	8.41	0.05
Standard error	3.23	1.71	0.01
Median	51.02	41.57	0.03
95% confidence interval	46.97 – 60.32	36.62 – 43.73	0.02 – 0.07
Maximum value	90.41	57.48	0.24
Minimum value	32.00	21.20	0.00

At first glance, the descriptive statistics do not favor good metabolic control of the examined group. The average TIR of 53.64% is not in agreement with the consensus recommendations of a minimum of 70.00%.[8] nor with the interpretations of the correlation between TIR and HbA1c.[11] Also, CV of 40.17% speaks of high glycemic variability in the group.[12] and AUC below the limit of 0.04 indicates that hypoglycemic episodes occured and with the obtained maximum AUC value of 0.24, we can assume that some of them were severe. However, the obtained decrease in laboratory-measured HbA1c tells us that there was an improvement during the study, and in further statistical processing we wanted to examine the correlation factors between the tested variables and laboratory-measured HbA1c after three months of using a professional system for continuous glucose monitoring. Table 3 shows the Pearson correlation's coefficient of HbA1c and all examined variables with each other, with statistical significance.

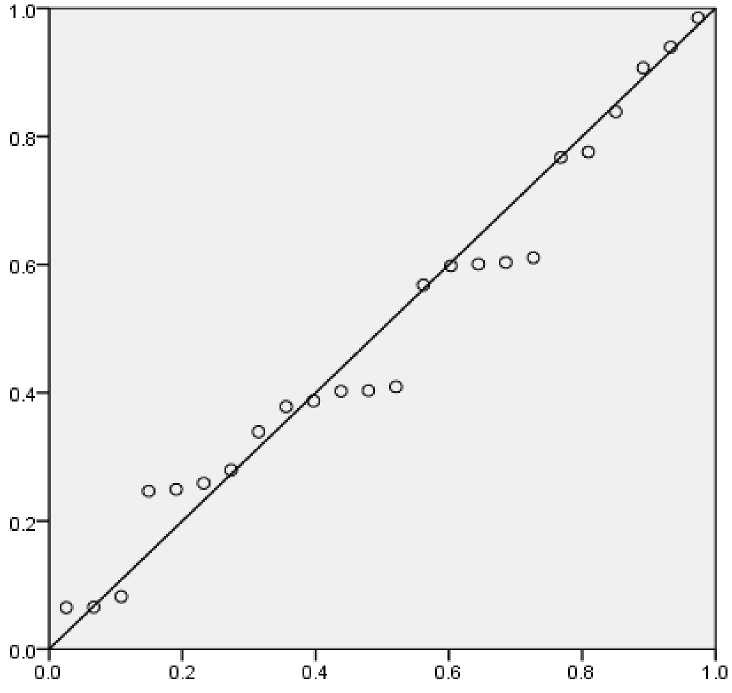
Table 3: Pearson correlation coefficient of examined variables.

		HbA1c	TIR	CV	AUC
HbA1c	Pearson coefficient p value	1	-0.699 p≤0.01	-0.064 p=0.767	-0.370 p=0.075
TIR	Pearson coefficient p value	-0.699 p≤0.01	1	-0.445 p≤0.05	0.000 p=1.00
CV	Pearson coefficient p value	-0.064 p=0.767	-0.445 p≤0.05	1	0.657 p≤0.01
AUC	Pearson coefficient p value	-0.370 p=0.075	0.000 p=1.00	0.657 p≤0.01	1

The highest correlation coefficient and the only one that shows statistical significance in connection with HbA1c is the time spent in the target range of TIR. This correlation is negative, which favors the fact that the higher the TIR, the lower the HbA1c.[11] Other variables do not correlate statistically significantly with HbA1c, but have statistically significant correlations with each other. CV correlates negatively with TIR and positively with AUC. This supports the fact that higher TIR means less glycemic variability, and therefore lower CV, and that higher CV means more hypoglycemic episodes, i.e. higher AUC below the limit. Correlation factors lead us to the conclusion that: increasing TIR, we decrease HbA1c, CV and the number and severity of hypoglycemic episodes.

A linear regression model of the dependence of HbA1c on these three variables was set up. The obtained R value of 0.820 ($R2=0.673$) tells us that the regression of HbA1c 67.3 % is influenced by these three variables, the most statistically significant of which is TIR ($t=-5.411$, $p\leq0.01$). Increasing the HbA1c by 1%, makes decrease the TIR of 4.5% in our group ($b=0.045$). The normal graph of the distribution of the observed and expected value of HbA1c in this model is shown in chart 1.

Chart 1. Observed value of HbA1c (x-axis), versus expected value of HbA1c (y-axis) in the set linear regression model.



As already stated in the text, the imperfection of the study itself, which affects the statistical analysis, is the small sample caused by the character of the tested group. The analysis itself, however, gave statistically significant results and links between the examined variables.

CONCLUSION

Subsequent statistical processing of the results showed that the decrease of HbA1c in the original research was most influenced by TIR, which coincides with modern methods and diagnostic recommendations.[8,10,11,15] CV, as well as AUC did not show a direct impact on HbA1c, but did show an impact on TIR, which can be explained by the imperfections of the research itself. The association of CV with AUC below the limit, which we took as a parameter for describing hypoglycemic episodes, is interesting. These two parameters are directly correlated, which means that a higher CV represents more hypoglycemic episodes. However, as a CV below 36% is considered good, we have to look at the AUC, or hypoglycemic episodes, even in these patients, because this does not mean that they are not present.[15]

Using a device for continuous glucose monitoring undoubtedly already gives good results in terms of therapeutic effect, but it also represents the future of diabetes therapy. The prevalence and wide use of these devices in therapy undoubtedly improves their metabolic control, however, clinicians must be aware of all the data obtained using these devices, know how to interpret them and, of course, with the still present gold standard HbA1c, determine the best course of therapy for the patient. Through statistical analysis in this paper, we have shown that all parameters are connected and that one depends on the other, so that a TIR of 70% does not mean that there is no variability or hypoglycemic episodes. The comprehensiveness of the image implies an overview of all parameters and their correct interpretation in order to avoid unwanted hypoglycemic episodes, which is particularly important in the pediatric population.[16]

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