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Relationship between Time in target and Glycosilated Haemoglobin in a cohort of Type 1 Diabetes paediatric patients with Continuous Glucose Monitoring vs Self-Monitoring Blood Glucose*

Relazione tra Time in Target ed Emoglobina Glicosilata in una coorte di pazienti pediatrici affetti da Diabete di Tipo 1 con monitoraggio glicemico in continuo vs automonitoraggio glicemico

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Abstract

OBJECTIVE OF THE STUDY In Type 1 Diabetes patients, Time in Target provides important glycometabolic control data and Glycosylated hemoglobin (HbA1c) could now be outdated by Time in Target. Some studies relating to the adult population with Type 1 Diabetes recognize the correlation between Time In Range (TIR%) and HbA1c%. The aim of this study is to evaluate this same relationship in a cohort of paediatric patients with Type 1 Diabetes using two different glycemic device.

DESIGN AND METHODS This is a retrospective observational study that evaluated 119 patients with Type 1 Diabetes (mean age 11,8±4,4), divided in two main groups, based on monitoring methods (66 CGM, 53 SMBG) and in two subgroups, based on insulin delivery methods (CSII or MDI). The aim was to find correlation between HbA1c% and Time in Target.

RESULTS HbA1c% - TIR% correlation was strongly in the CGM group and moderate in SMBG one. For an increase of TIR of 10%, HbA1c% reduced of 0.45 in the CGM group and 0.31 in the SMBG one. As further results we found that in CGM and SMBG groups the correlation between TDD and HbA1c resulted statistically significant (an increase of TDD corresponding with an increase in HbA1c) and that insulin delivery method (CSII

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All study participants and their parents or legal guardians provided informed consent to anonymous data collection, analysis, and publication for research purposes. Ethical review is not required for studies involving only retrospective observational data and/or data collected as part of routine patient care.

or MDI) influences TDD only in CGM group: CSII=33 IU (±16,62) vs MDI= 19,5 IU (±16,37) and doesn't influence HbA1c%: in CGM group CSII=7.4% (±1.08) vs MDI=7.7% (±1.00). In SMBG group: CSII=8.35% (±1.88) vs MDI=8.00% (±1.24).

CONCLUSIONS In line with the literature, for each increase of 10% in TIR there is a reduction of HbA1c values; in our study, HbA1c% changes by 0.45 in the CGM group and 0.31 in the SMBG group with inference on pediatric population. Furthermore, the use of CSII involves an increase in the TDD.

KEY WORDS type 1 diabetes; technology applied to diabetes; paediatrics; continuous glucose monitoring.

Riassunto

OBIETTIVO DELLO STUDIO Nei pazienti affetti da diabete di tipo 1 il Time in Target fornisce importanti dati sul controllo glicometabolico e può sicuramente affiancare, e forse in futuro sostituire, l'Emoglobina glicosilata. Nella popolazione adulta con diabete di tipo 1 la correlazione tra Time in Range (TIR%) e HbA1c è ormai un dato acquisito. Obiettivo di questo studio è valutare questa stessa relazione in una coorte di pazienti pediatrici con diabete di tipo 1 che usa due differenti sistemi di monitoraggio glicemico.

DISEGNO E METODI È uno studio osservazionale retrospettivo che ha valutato 119 pazienti affetti da diabete di tipo 1 (età media 11,8±4,4), divisi in due gruppi principali in base al sistema di monitoraggio glicemico utilizzato (66 CGM, 53 SMBG) e in due sottogruppi in base al metodo di erogazione dell'insulina (CSII or MDI). L'obiettivo è stato trovare una correlazione tra HbA1c e Time in Target.

RISULTATI La correlazione tra HbA1c% - TIR% è forte nel gruppo CGM e moderata in quello SMBG. Per un incremento del TIR del 10%, l'HbA1c% si reduce di 0.45 nel gruppo CGM e di 0.31 nel gruppo SMBG. Come risultati collaterali abbiamo evidenziato che nei gruppi CGM e SMBG la correlazione tra TDD e HbA1c% è risultata statisticamente significativa (un aumento della TDD corrisponde a un incremento dell'HbA1c%) e che il metodo di erogazione dell'insulina (CSII o MDI) influenza la TDD solo nel gruppo CGM: CSII=33 IU (±16,62) vs MDI= 19,5 IU (±16,37). Non influenza invece l'HbA1c%: nel gruppo CGM con CSII=7.4% (±1.08) vs MDI=7.7% (±1.00). Nel gruppo SMBG: CSII=8.35% (±1.88) vs MDI=8.00% (±1.24).

CONCLUSIONI In linea con la letteratura, ad ogni aumento di TIR del 10% si associa una variazione dell'HbA1c% di 0.45 nel gruppo CGM e 0.31 nel gruppo SMBG, con inferenza sulla popolazione pediatrica. Inoltre, l'utilizzo del CSII comporta un aumento della TDD.

PAROLE CHIAVE diabete tipo 1; tecnologia applicata al diabete; pediatria; monitoraggio glicemico in continuo.

Introduction

The concept of glucose monitoring is changed after Continuous Glucose Monitoring (CGM) innovation, especially in pediatric population. CGM reports give to the diabetologist, patients and caregiver several data upon which to target insulin doses and enterprise strategies to modify behaviour in Type 1 Diabetes patients (T1D). ADA and ISPAD endorsed CGM use in all Type 1 Diabetes patients of all age.[1,2]

HbA1c represents the gold standard to evaluate the glycaemic trend of the last three months of Type 1 Diabetes patients and predicts a long -last-term complications. For each HbA1c value, there are a wide range of mean glycaemic values. For example: HbA1c of 8% (64 mmol/mol) could be associated with a good, moderate or worst glycaemic control as highlight from mean glycaemic values between 128 mg/dL and 249 mg/dL, corresponding to HbA1c of 8% (64 mmol/mol).[3]

HbA1c doesn't consider individual variables, conditions, or pathologies such as haemolytic anaemia, haemoglobinopathies, pregnancy, haemorrhagic disease in which HbA1c could be lower than real. Furthermore, HbA1c reflects the turnover of red blood cells and glycation process, and it could be possible to estimate the HbA1c through equations.[4]

In patients with several hypoglycaemic episodes, HbA1c is lower. Therefore, HbA1c estimates hyperglycaemia but doesn't give information about hypoglicaemia, glycaemic variability or power and frequency of glycaemic variability within a day. A goal of HbA1c around 7% (58 mmol/mol) is desirable for children and adolescent but difficult to achieve.[1,5,6] HbA1c target is a challenge to keep glucose in target avoiding hypoglycaemia.[7]

In the paediatric population, diabetes management was prior focused on avoiding hypoglycaemia. Actually, there is evidence about both glycaemic excursions and high glucose levels that cause detri-

mental effects on the developing brain of children, suggesting the importance to mitigate exposure to hyperglycaemia and frequent glucose fluctuations. [6–8]

HbA1c remains one of the most important parameters of glycometabolic control and is a good predictor of micro-vascular complications, as well as the TIR%. Beck et al. [9] used DCCT study data [10] and measured association between TIR (70-180 mg/dl) and long term risk of complications (retinopathy and microalbuminuria). For each 10% of increase of TIR, there is an increase of 40% of microalbuminuria and 64% of retinopathy). [9] Consensus ATTD (2019) standardized "CGM metrics for clinical care" expressing glycaemic values within the reference range: Time in Range (TIR), Time Above Range (TAR), Time Below Range (TBR), that show the percentage of time spent in those range values.[12] Furthermore, there have been recommended goals for "time in target" for each category of patients (Type 1 and 2 diabetes, gestational diabetes, and high or low-risk patients). Glucose metrics, including time spent in the range (70–180 mg/dL [3.9-10.0 mmol/L], TIR), below the range (<70 mg/dL) [3.9 mmol/L], TBR), above range (>180 mg/dL [10 mmol/L], TAR) and coefficient of variation (CV) [13] can be used as outcomes, to make specific therapeutic decisions, improve communication between healthcare providers, looking together the same report, recommending specific values for each Time in Target.[12,14]

In literature, there are some studies that evaluate the correlation between Time in Target and HbA1c. Beck et al. [11] analysed four studies: JDRF Continuous Glucose Monitoring RCT [15], DIAMOND [16], REPLACE-BG [17], HypoDE [18] performed on adult Type 1 Diabetes patients who used different devices.

In patients who wear Continuous Glucose Monitoring, TIR% provides robust data on the patient's glycometabolic control and represents a measure to predict long-term complications, as well as HbA1c. Beck et al. [9] used the data of DCTT study [10] and measured the association between TIR (70-180 mg/dl) and development of long-term complications (development or progression of retinopathy and microalbuminuria in the adult population). They showed that for each reduction of 10% of TIR there was an increase of microalbuminuria of 40% (95% CI 25-56). As regard as the correlation between HbA1c and TIR%, Vigersky and McMahon [19] analyzed an adult population with Type 1 and 2 Diabetes and showed that for each variation of 10% of TIR there is a change in HbA1c of 0,8%. Indeed, Beck et al. [9] estimate that in a Type 1 Diabetes population (adults and children), for each reduction of 10% of TIR there is a change of 0,5% of HbA1c.

Parents used CGM as a tool to avoid hypoglycaemia risk [20] but not to manage hyperglycaemia. [21]

In this study two different glycaemic monitoring devices and two different infusion delivery modes were compared: Self-Monitoring Blood Glucose (SMBG) vs CGM and Continuous Subcutaneous Insulin Infusion (CSII) vs Multiple Daily Injection (MDI). The goal is to find a significant correlation between Time In Range and HbA1c in a pediatric population using only one type of device. Total MARD in pediatric age of RT-CGM Dexcom G6 is 7,7% [22, 23] according to International Consensus on Use of CGM.[11] Dexcom G6 maintains constant accuracy levels during all sessions of sensor (10 days) and in all situations of glycaemic variation.[24]

Study design and methods

The hypothesis testing of this study regarded the existing correlation between TIR and HbA1c and the aim of the study was to analyse how HbA1c is influenced by Time in Target in the two groups through correlation measure and linear dependence.

In this retrospective study we have chosen only patients who wear DEXCOM G6 device because it is the most used in our diabetology unit and to reduce bias due to other sensor's structure. All informed consents were obtained from patients' parents. Data were collected from a cohort of children with Type 1 Diabetes conducted to the Diabetologic ambulatory from January to October 2020 and divided in subgroup based on the device worn and mode of insulin delivery. 119 patients with Type 1 Diabetes 0-18 years old (mean age 11,8±4,4) were enrolled and the entire sample was divided in two main groups, one of 66 patients in CGM (DEXCOM G6) and the second group (53 patients) in SMBG. These two groups were further divided into two subgroups by insulin delivery (CSII or MDI). Demographic features are reported in table 1. For each group, HbA1c%, Time on Target (TIR%, TAR%, TBR%) and Total Daily Dose were evaluated.

In the SMBG group device data for 15 days before the day of visit were downloaded and the same day laboratory HbA1c was performed. Even if the literature suggests analyzing data with at least 7/day capillary measures [25], the average of the measures of our patients was 4,9/day. All values of Time in Target

Table 1 | Demographic sample features.

Variables	Insulin delivery	SMBG	CGM
N patients	CSII MDI	10 43	29 37
Male (N)	CSII MDI	5 18	9 19
Mean age	CSII MDI	15,3 11,7	12,3 10,2
Duration of di etes (y)	CSII MDI	6,3 4,1	6,6 3,4

were distributed (Table 2). Patients performed basal bolus scheme insulin therapy with the number of injections from 4 to 6 per day.

Ambulatory Glucose Profile (AGP) reports of CGM group were analyzed for 14 days period before the day of visit, according to the literature [26], and the same day laboratory HbA1c was performed. The platform in the cloud where we analyzed the data was DEXCOM CLARITY. We considered all CGM metrics (Consensus ATTD 2019).

Statistical analysis was performed using R Software 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and to test the hypothesis of the study we used the Shapiro test, Wilcoxon test, and linear regression model. Shapiro test was used to determine whether continuous variables were normally distributed. Variables with a non- normal distribution were evaluated using the Wilcoxon test and the results are presented as P values.

Results

we analyzed HbA1c% and TIR% variables in CGM group. The negative correlation between variables were statistically significant (p-value = 2.836e-13=0, r= -0.7536154), IC95% [-0.84; -0.63] and through a linear regression model we found an estimated equation in CGM group: HbA1c (%) = 9.96 - 0.045*TIR (%), b = -0.045±0.0049; p-value=2.84e-13=0. TIR has a significant effect on HbA1c. For each 10% of increase of TIR, there is a variation of 0,45% of HbA1c (Figure 1). This model explains 57% of HbA1c variability.

In SMBG group (p-value = 6.255e-05=0, r=-0.5303524), there is a moderate negative correlation, IC95% [-0.70; -0.30]. We found an estimate equation: HbA1c (%) = 9.80 - 0.031*TIR (%), beta = -0.031±0.0071; p-value=6.26e-05=0. TIR has a significant effect on HbA1c. For each 10% of increase of TIR, there is a variation of 0,31% of HbA1c. (Figure1). This model explains 28% of HbA1c variability.

Analyzing the median variables (TDD, TIR, TBR, TAR, HbA1c) related to 4 subgroups (CGM-MDI/CSII and SMBG- MDI/CSII) with a non-parametric test of Kruskal Wallis, only for Total Daily Dose and TBR variables significant results were found.

As secondary results we found a linear and posi-

Table 2 | SMBG and CGM metrics characteristics. All values are expressed as average± standard deviation. NA: Not applicable.

	SMBG group	CGM group
N test/ day	4,85±0,83	NA
Mean blood glucose	170,40±36,02	190,47±30,92
TIR%	54,88±20,80	47,18±17,17
TAR%	41,07±21,41	50,79±17,84
TBR%	4,02±5,50	1,53±1,95
CV%	NA	34,4±6,34
Time use of sensor %	NA	91,74±8,69
GMI%	NA	8,25±0,010

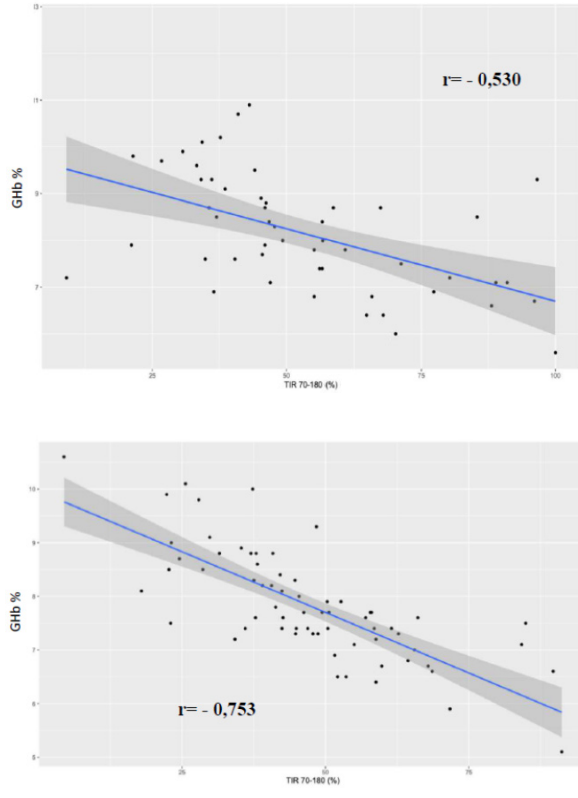

Figure 1 | Linear regression between HbA1c % (GHb%) and TIR% 70-180 in SMBG and CGM group.

tive correlation statistically significant between HbA1c and TDD in CGM group (p-value = 0.0044, r=0,346), IC =95%[0.114; 0.543] and in SMBG group (p-value = 0.02344, r= 0,311), IC 95% [0.044; 0.536] (Figure 2) and that insulin delivery method (CSII or MDI) influences TDD only in CGM group: CSII=33 IU (±16,62) vs MDI= 19,5 IU (±16,37) and doesn't influence HbA1c%: in CGM group CSII=7.4% (±1.08) vs MDI=7.7% (±1.00). In SMBG group: CSII=8.35% (±1.88) vs MDI=8.00% (±1.24).
(Figures 3, 4) In each group we observe that the variable TDD is lower in MDI subgroup compared to CSII, especially in CGM group.

Discussion

As concerned as Time in Target, as highlight by the literature, HbaA1c is negatively correlated to Time in Range 70-180 mg/dl, especially in CGM group. Intuitively, people will spend more time in euglycaemia having lower HbA1c values. In our study for each 10% of increase of TIR, HbA1c% will be reduced by 0,45% in CGM group and 0,31% in SMBG one. As regard as TIR and HbA1c analysis correlation, an Italian study, that enrolled 654 children and adolescents in five Regional Centres for Paediatric Diabetes, confirmed a strong

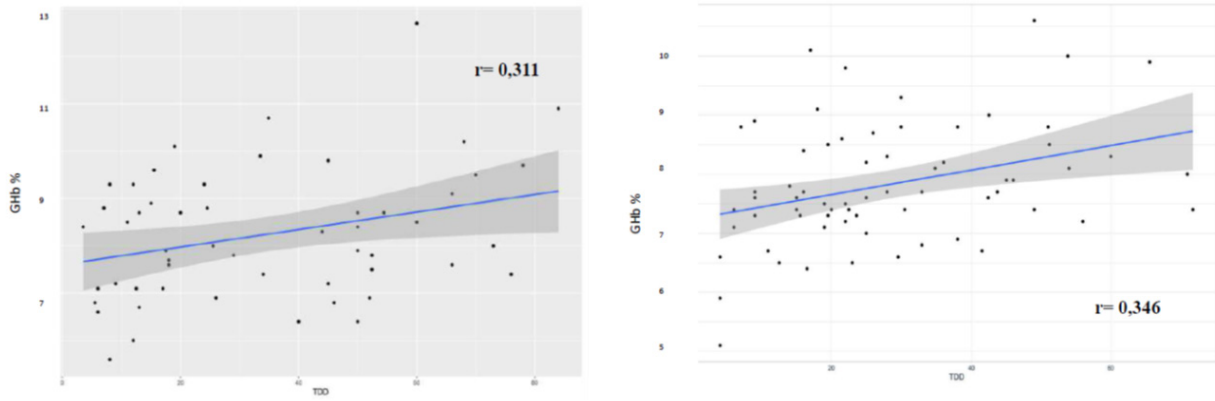

Figure 2 | Linear regression between HbA1c % (GHb%) and Total Daily Dose in SMBG and CGM.

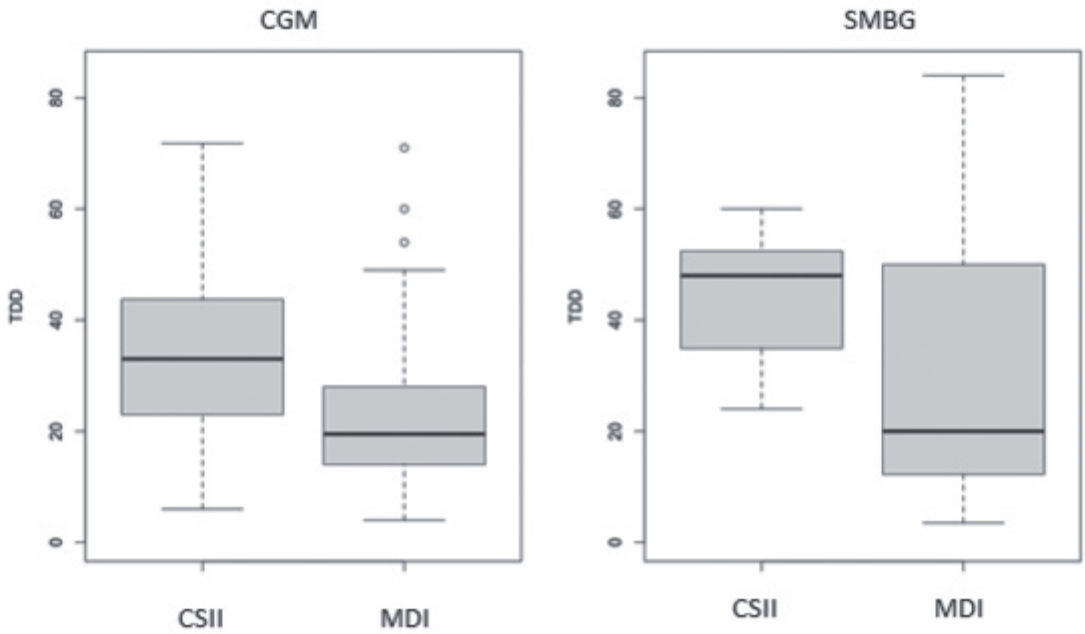

Figure 3 | Boxplots about relationship between Total Daily Dose and infusion delivery mode.

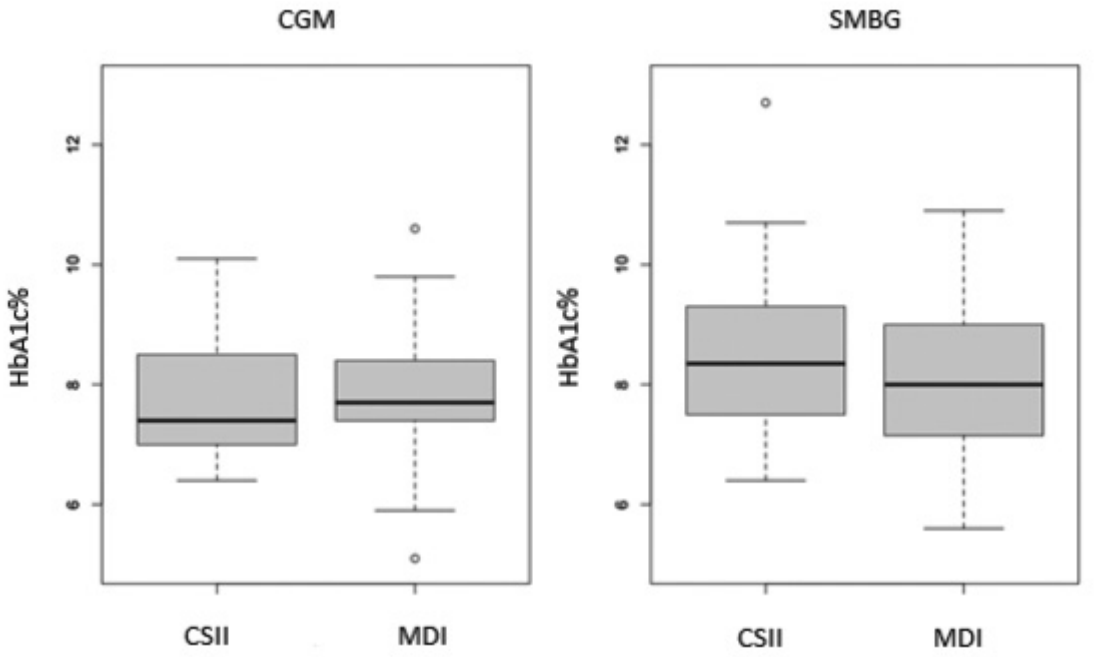

Figure 4 | Boxplots about relationship between HbA1c %(GHb%) and infusion delivery mode.

and negative correlation between these two variables [27] but they used data from different device, HbA1c was measured in different laboratories and the population examined was heterogeneous from different regions. We have instead analyzed a pediatric population of a single Centre for Paediatric Diabetes and with a single specific device (Dexcom G6) to avoid bias due to different sensor (specific MARD%, different calibration). In table 3 we evaluate the specific TIR%-HbA1c% correlation and this analysis has inference on pediatric population who wear Dexcom G6.

Analyzing the other CGM metrics, in the post hoc analysis of TBR variables patients with a lower TBR are the ones where they use CGM, both in CSII and in MDI. This result could be explained because who uses CGM is able to prevent hypoglycaemia, thanks to trend arrows. For SMBG group, there isn't a significant divergence but only a trend to spend less time in TBR in CSII subgroup (precision insulin delivery through carbo-counts, manual suspension of basal insulin delivery in case of hypoglycaemia and temporary basal profile could be some of the reasons).

As regard as TDD variables, we observed that TDD values in MDI patients are usually lower than CSII ones. Despite of the lower dose of insulin and regardless of the glycaemic monitoring device used, patients with MDI have not a worse glycaemic control. In fact, HbA1c median values don't change between the two main groups. Unexpectedly, HbA1c variable correlates positively with TDD variables (at the increase of TDD increases the HbA1c). It is difficult to explain which type of population (prepubertal or pubertal) appears in this correlation; considering the mean age of the sample is reasonable to deduce that in adolescents there is often no good metabolic control and therefore they increase the insulin dose to compensate for this; furthermore in the prepubertal stage there is a common insulin resistance linked to changes in the hormonal structure typical of this age.

Unlike other studies in the literature [11, 20], ours includes only a Type 1 Diabetes pediatric population that uses a single device model (DEXCOM G6), evaluating Clarity AGP reports to minimize bias due to different algorithms[28,29], age, and type of diabetes. TIR% and HbA1c% correlation related to the paediatric population who use this sensor device was reported in table 3. This table could be of support to health providers for more accurate monitoring of therapy and to avoid quarterly venous blood sampling for HbA1c in Type 1 Diabetes children. Beck et al. [10] used a data set that included 7-point profiles collected every 3 months during the DCCT trial that represents a big data set. In this study, we used data from 43 subjects over 15 days with less information compared to DCCT with a limitation of our study.

Table 3 | HbA1c% and TIR% correlation in CGM and SMBG group.

TIR	Theory HbA1c Laboratory		IC95%	IC95%
	CGM	SMBG	CGM	SMBG
0%	9,96% (85 mmol/mol)	9,8% (84 mmol/mol)	(9,96%-9,96%)	(9,8%-9,8%)
10%	9,51% (80 mmol/mol)	9,49%(80 mmol/mol)	(9,41%-9,61%)	(9,35%-9,63%)
20%	9,06% (76 mmol/mol)	9,18% (77 mmol/mol)	(8,87%-9,25%)	(8,9%-9,46%)
30%	8,61% (71 mmol/mol)	8,87% (73 mmol/mol)	(8,32%-8,9%)	(8,45%-9,29%)
40%	8,16% (66 mmol/mol)	8,56% (70 mmol/mol)	(7,78%-8,54%)	(8,00%-9,12%)
50%	7,71% (61 mmol/mol)	8,25% (67 mmol/mol)	(7,23%-8,19%)	(7,55%-8,95%)
60%	7,26% (56 mmol/mol)	7,94% (63 mmol/mol)	(6,68%-7,84%)	(7,11%-8,77%)
70%	6,81% (51 mmol/mol)	7,63% (60 mmol/mol)	(6,14%-7,48%)	(6,66%-8,60%)
80%	6,36% (46 mmol/mol)	7,32% (56 mmol/mol)	(5,59%-7,13%)	(6,21%-8,43%)
90%	5,91% (41 mmol/mol)	7,01% (53 mmol/mol)	(5,05%-6,77%)	(5,91%-8,26%)
100%	5,46% (36 mmol/mol)	6,7% (50 mmol/mol)	(4,5%-6,42%)	(5,31%-8,09%)

Conclusions

In conclusion, HbA1c is at the current time the gold standard to evaluate glycometabolic control of diabetes, but it is likely that soon TIR% and other CGM metrics will be more useful and complete than HbA1c. This study has highlighted the close correlation, with inference on a specific population, the pediatric one using the DEXCOM G6 sensor, between TIR% and HbA1c%, and the related table can be useful in clinical practice.

Abbreviations

SMBG–Self Monitoring Blood glucose
CGM - Continuous glucose monitoring
CV - Coefficient of variation
TAR - Time above the range >180 mg/dL (10 mmol/l)
TBR - Time below the range <70 mg/dL (3.9 mmol/l)
TIR - Time in range 70–180 mg/dL (3.9–10 mmol/l)
CSII - continuous subcutaneous insulin infusion – insulin pump therapy
MDI - Multiple Daily Injections
HbA1c - Glycated Hemoglobin
MARD - Mean Absolute Relative Difference
ADA - American Diabetes Association
ISPAD - International Society for Paediatric and Adolescent Diabetes

Punti chiave

- Anche se al momento attuale l'HbA1c rimane il gold standard per la valutazione del controllo glicometabolico nel diabete, il TIR% e le altre metriche CGM sono più utili e complete.
- Probabilmente, il TIR% e le altre metriche CGM sostituiranno a breve l' HbA1c.
- Il monitoraggio glicemico in continuo rappresenta indubbiamente un valore aggiunto nella gestione del diabete di tipo 1 in pediatria.
- Questo studio ha evidenziato la stretta correlazione tra TIR% e HbA1c, con inferenza nella popolazione pediatrica che usa DEXCOM G6.
- È stata prodotta una relativa tabella che può risultare utile al diabetologo pediatra nella sua pratica clinica.

Key points

- Even if HbA1c is at the current time the gold standard to evaluate glycometabolic control of diabetes, TIR% and other CGM metrics are more useful and complete than HbA1c.
- Probably, TIR% and other CGM metrics will replace HbA1c shortly.
- Glycaemic continuous monitoring undoubtedly represents an added value in the management of Type 1 diabetes in pediatrics.
- This study has highlighted the close correlation, with inference on pediatric population using the DEXCOM G6 sensor, between TIR% and HbA1c%.
- A related table that is useful in clinical practice has been extrapolated.

Bibliografia

1. Sundberg F, Barnard K, Cato A, et al. Managing diabetes in preschool children. Pediatr Diabetes 18:499–517, 2017.
2. Sherr JL, Tauschman M, Battelino T, et al. ISPAD Clinical Practice Consensus Guidelines 2018 Diabetes Technologies. Pediatr Diabetes 2018.
3. Beck RW, Connor CG, et al. The Fallacy of Average: How Using HbA1C Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care 40:994–999, 2017.
4. Kovatchev BP. Metrics for glycaemic control - from HbA1c to continuous glucose monitoring. Nat Rev Endocrinol 13:425-436, 2017.
5. Dimeglio LA, Acerini CL, Codner E, et al. Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes 2018 ISPAD Clinical Practice Consensus Guidelines 105–14, 2018.
6. American Diabetes Association. Children and adolescents: Standards of medical care in diabetes—2021. Diabetes Care 44:S180–99, 2021.
7. Gerhardsson P, Schwandt A, Witsch M, et al. The SWEET project: 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. Diabetes Technol Ther, 2021.
8. Mauras N, Buckingham B, White NH, et al. Impact of Type 1 Diabetes in the Developing Brain in Children: A Longitudinal Study. Diabetes Care dc202125, 2021.
9. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, Close KL. Validation of Time in Range as an Outcome Measure for Diabetes Clinical TrialsDiabetes Care 42:400-405, 2019.
10. The Diabetes Control and Complications Trial Research Group. DCCT, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. NEJM 329:977-986, 1993.
11. Beck RW, Bergenstal RM, Cheng P, et al. The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c. J Diabetes Sci Technol 13:614-626, 2019.
12. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care 42:1593–603, 2019.
13. Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 21;40:1631–1640, 2017.
14. Bergenstal RM, Ahmann AJ, Bailey T, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP). Diabetes Technol Ther 15:198–211, 2013.
15. Juvenile Diabetes Research Foundation Continuous Glucose MonitoringStudy Group. Effectiveness of Continuous Glucose Monitoringin a clinical care environment: evidence from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring(JDRF-CGM) trial. Diabetes Care 33:17-22, 2010.
16. Beck RW, Riddlesworth T, Ruedy K, et al. DIAMOND Study Group. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 317:371-378, 2017.
17. Aleppo G, Ruedy KJ, Riddlesworth TD, et al. REPLACE-BG: A Randomized Trial Comparing Continuous Glucose MonitoringWith and Without Routine Blood Glucose Monitoring in Adults With Well-Controlled Type 1 Diabetes. Diabetes Care 40:538-545, 2017.
18. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time Continuous Glucose Monitoringin adults with Type 1 Diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 391:1367-1377, 2018.
19. Robert A. Vigersky and Chantal McMahon. The relationship of Hemoglobin A1c to Time in Range in patients with diabetes. Diabetes technology & Therapeutics Diabetes TechnolTher 21:81-85 2019.
20. Mauras N, Beck R, Xing D, et al. A randomized clinical trial to assess the efficacy and safety of real-time Continuous Glucose Monitoringin the management of Type 1 Diabetes in young children aged 4 to <10 years. Diabetes Care 35:204–10, 2012.
21. Di Meglio LA, Kanapka LG, DeSalvo DJ, et al. A Randomized Clinical Trial Assessing Continuous Glucose Monitoring(CGM) Use With Standardized Education With or Without a Family Behavioural Intervention Compared With Finger-stick Blood Glucose Monitoring in Very Young Children With Type 1 Diabetes. Diabetes Care dc201060, 2020.
22. Welsh JB, Zhang X, Puhr SA, et al. Performance of a Factory-Calibrated, Real-time Continuous Glucose MonitoringSystem in Pediatric Participants With Type 1 Diabetes. J Diabetes Sci Technol 13:254-258, 2019.
23. Shah VN, Laffel LM, Wadwa RP, et al. Performance of a Factory-Calibrated Real-time Continuous Glucose MonitoringSystem Utilizing an Automated Sensor Applicator.DiabetesTechnolTher 20:428-433, 2018.
24. Wadwa RP, Laffel LM, Shah VN, et al. Accuracy of a Factory-Calibrated, Real-Time Continuous Glucose Monitoring System During 10 Days of Use in Youth and Adults with Diabetes. DiabetesTechnolTher 20:395-402, 2018.
25. Mazze RS, Lucido D, Langer O, et al. Ambulatory glucose profile: representation of verified self-monitored blood glucose data. Diabetes Care 10:111–117, 1987.
26. Riddlesworth TD, Beck RW, Gal RL, et al. Optimal Sampling Duration for Continuous Glucose Monitoringto Determine Long-Term GlycemicControl.DiabetesTechnolTher 20:314-316. doi: 10.1089/dia.2017.0455, 2018.
27. Piona C, Marigliano M, Mozzillo E, Rosanio F, Zanfardino A, Iafusco D, Maltoni G, Zucchini S, Piccinno E, Delvecchio M, Maffeis C. Relationships between HbA1c and continuous glucose monitoring metrics of glycaemic control and glucose variability in a large cohort of children and adolescents with type 1 diabetes. Diabetes Res Clin Pract 177:108933. doi: 10.1016/j.diabres.2021.108933. Epub 2021 Jun 30. PMID: 34216681, 2021.
28. Nathan DM, Kuenen J, Borg R, et al. A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 31:1473-8, 2008.
29. Johnson ML, Martens TW, et al. Utilizing the Ambulatory Glucose Profile to Standardizeand Implement Continuous Glucose Monitoringin Clinical Practice. Diabetes Technology & Therapeutics 21, Supplement 2, 2019.