Acta Biomed 2018; Vol. 89, Supplement 5: 22-26 DOI: 10.23750/abm.v89iS4.7357

Original article

Translating the HbA1c assay into estimated average glucose values in children and adolescents with type 1 diabetes mellitus

Ahmed Sayed[1], *Fawzia Alyafei*[1], *Vincenzo De Sanctis*[2], *Ashraf Soliman*[1], *Mona Elgamal*[1]

[1] Department of Pediatrics, Hamad Medical Center, Doha, Qatar; [2] Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy

Summary. *Objective:* The A1c assay, expressed as the percent of hemoglobin that is glycated, measures chronic glycemia and is widely used to judge the adequacy of diabetes treatment and adjust therapy. Day-to-day management is guided by self-monitoring of capillary glucose concentrations (milligrams per decilitre or millimoles per litter) as well as by using continuous glucose monitoring systems (CGMS). We found a mathematical relationship between A1c and average glucose (AG) levels measured by CGMS over 5 days and determined the correlation between the variable CGMS parameters and HbA1c in 50 children with type 1 diabetes mellitus (DM-1) on MDI therapy. *Research design and methods:* A total of 50 diabetic children randomly selected from a cohort of children with DM-1 were included in the analyses. A1c levels obtained at the end of 3 months and measured in a central laboratory were compared with the AG levels during the previous 5 days recorded by CGMS. AG was calculated by combining weighted results from 5 days of continuous glucose monitoring performed before measuring HbA1c, with 3-5 point daily self-monitoring of capillary (fingerstick) glucose. *Results:* Linear regression analysis between the A1c and AG values provided the tightest correlations HbA1c=0.0494 MG- 2E-14, R2=0.90, *P*<0.0001), allowing calculation of an estimated average glucose (eAG) for A1c values. *Conclusions:* Our study showed a linear relationship between HbA1C and AG values measured by CGMS for 5 days before HbA1c measurement. The AG can be easily calculated using a formula derived from linear regression analysis of HbA1c data obtained in our diabetic children. (www.actabiomedica.it)

Key words: type 1 diabetes mellitus, children, adolescents, glycated hemoglobin, continuous glucose monitoring system

Introduction

Clinical trials have demonstrated the association between HbA1c and both microvascular and macrovascular complications in type 1 diabetes mellitus (DM-1) (1). HbA1c estimates glucose level over the previous 2-3 months, while the continuous glucose monitoring (CGM) devices measure continuous glycemic profile over a few days and provide many information including patterns, trends and time of glucose changing. In meta-analysis studies real-time CGM appears more effective than self-monitoring of blood glucose (SMBG) in type 1 diabetes (2, 3).

The relationship between the monitoring of blood glucose (MBG) level and HbA1c has been examined in several studies, most of the studies either emphasis on infrequent capillary glucose measurements (4-6). We recorded and analyzed the level of HbA1c in rela-

tion to different glucose parameters over 5 days and measured the 24 h mean blood glucose (MBG) from in 50 children with type 1 diabetes mellitus (DM-1). Correlation studies were performed between glucose parameters measured by CGMS and HbA1c level.

Patients and Methods

Fifty randomly selected children with type 1 DM (aged between 3 and 15 years) were included in this study. They had the onset of DM-1 for more than 6 months and were able to perform finger stick glucose testing four times daily.

All children had normal thyroid function and had no other systemic illness or syndrome.

The Medtronic (Northridge, CA) MiniMed CGMS® Gold sensor was used as the CGMS in all children for 5 days prior to measuring HbA1c. Children and their parents were instructed to enter their daily blood glucose finger sticks (morning, lunch, dinner, and before bedtime) into the device for calibration, and children were blinded to the sensor reading. All participants completed CGMS for 5 consecutive days before testing their HbA1c levels. The 24 h mean blood glucose (MBG) and glucose standard deviation values (GSD), BG concentrations before and 2 h after breakfast, lunch and dinner, and the number of high (>250 mg/dL) and low (<60 mg/dL) excursions were recorded.

The study was approved by the IRB committee of Hamad Medical Centre before performing the study.

Spearman correlations and linear regression analyses were applied to quantify the relationship between HbA1C and glucose markers.

Results

The glycemic parameters measured by CGMS 5 days before measuring HbA1c in our 50 children with DM-1 with variable glycemic control are reported in table 1. In particular, 24 h MBG was positively correlated with HbA1c (r=0.90, P<0.001) in all children with DM-1. In addition, the HbA1c was correlated significantly with BG standard deviation score (SDS), BG before and after breakfast and BG after lunch (Table 2 and Figures 1-3).

Discussion

Along with its role in diagnosing diabetes, the A1c test is performed between 2 and 4 times per year to estimate average blood sugar levels over the previous

Table 2. Correlation between HbA1c and CGMS glycemic data

	R	p
MG	0.90	0.00001**
GSD	0.43	0.026*
G before breakfast	0.450362	0.014
G after breakfast	0.543387	0.0023 *
G before lunch	0.340357	0.070
G after lunch	0.406634	0.028*
G before dinner	0.218728	0.254
G after dinner	0.343988	0.067
MAD	0.079114	0.683
Number of largest excursions	0.196	0.12
Number of lowest excursions	0.410241	0.027*

* P<0.05, ** P<0.001; Abbreviations: Mean G=mean glucose for 5 days, GSD=glucose standard deviation values, MAD=median absolute percent difference (denoting glucose variability) and A1C level.

Table 1. Glucose parameters during the 5 days and HbA1c levels

	Age	G before BF	G beforelunch	G before dinner	Mean G	G SD	highest G	MAD%	No highest EX	No Lowest EX	G after BF	G after lunch	G after dinner	lowest G	HA1C
	yr	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L		per 5 days	per 5 days	mmol/L	mmol/L	mmol/L	mmol/L	%
Mean	12.38	140.81	168.77	168.41	170.55	57.62	300.88	14.69	7.26	2.60	198.91	179.89	176.10	82.88	9.12
Standard Error	1.18	11.13	13.40	15.03	10.17	5.14	16.77	1.31	0.69	0.36	15.36	13.24	14.71	15.91	0.44
Median	12.00	116.00	139.00	143.00	154.00	58.50	350.00	12.65	8.00	2.00	189.00	174.50	178.00	64.00	9.20
SD	7.68	67.69	83.68	80.93	65.92	33.30	108.66	8.51	4.49	2.36	90.85	79.42	79.23	103.09	2.84

Abbreviations: G = glucose, BF = breakfast, Mean G = mean glucose for 5 days, MAD %= median absolute percent difference.

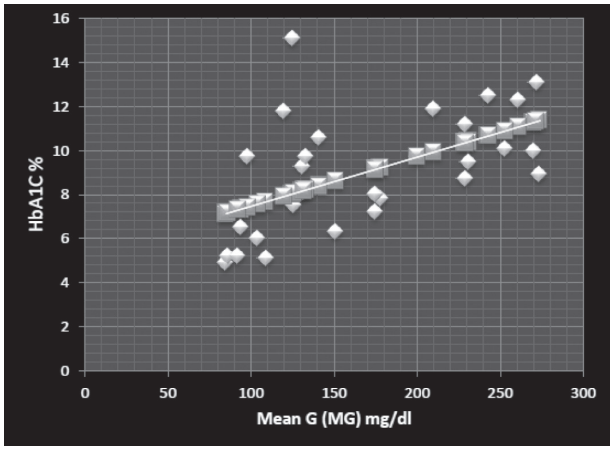

Figure 1. Regression of mean glucose (MG) (mg/dL) and HbA1c level

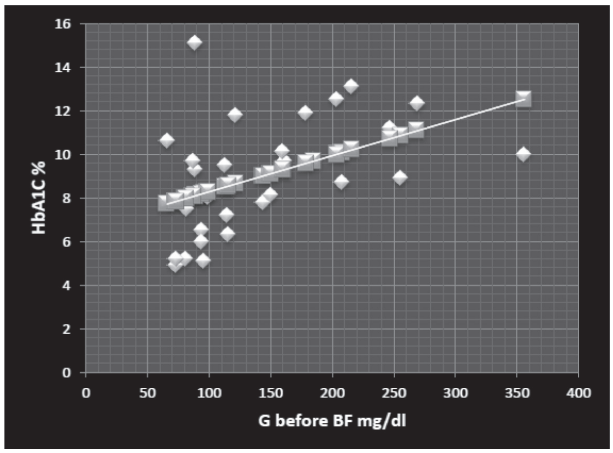

Figure 2. Regression of mean glucose (G) (mg/dL) before breakfast and HbA1c level

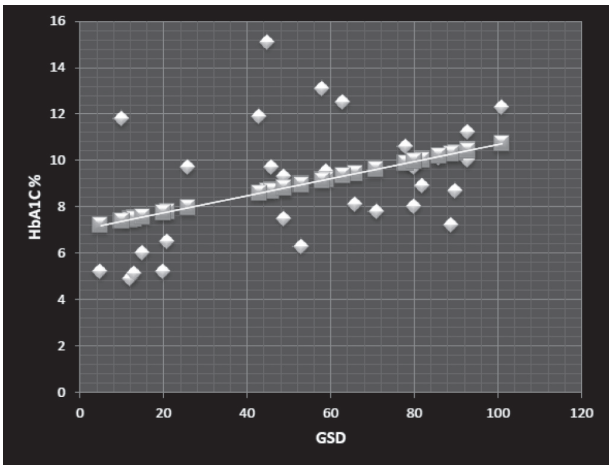

Figure 3. Regression of GSD (glucose standard deviation values, mg/dL) and HbA1c level

3 months. This test is used to monitor the effectiveness of diabetes treatment and to determine if overall blood sugar goals are being met. The American Diabetes Association recommends a target A1c below 7.5% in children with diabetes, which is an average blood glucose concentration (eAG) below 170 mg/dl (7-11). In the DCCT study, retrospective analysis of data derived from SMBG measurements identified a linear correlation between HbA1c and eA. However, the correlation was based on only on fingerstick glucose measurements (7, 8). The ADAG study defined a mathematical equation between HbA1c and the eAG level (eAG mg/dL=28.7×HbA1c–46.7), which has been widely used in the clinical practice and the equation was recommended by the ADA's calculation of the eAG. In ADAG study, participants underwent CGM for 48 hours at baseline and monthly for the duration of the study, as well as the SMBG measurement 7 times per day for at least 3 days per week. Over the course of the 12-week study, approximately 2.700 glucose measurements were performed on each participant (8).

In our study, the linear equation showed that HbA1c=0.0494 MG- 2E-14. Accordingly, the predicted HbA1c based on this equation is reported in table 3.

Table 3.

Our data based on our equation		Published data (Ref. 8)	
HbA1c %	AG mg/dL	HbA1c	AG mg/dL
4	80		
4.446	90		
4.94	100		
5.4	110		
5.9	120	6	126
6.4	130	6.5	140
6.9	140	7	154
7.4	150	7.5	169
7.9	160	8	183
8.4	170	8.5	197
8.9	180	9	212
9.4	190	9.5	226
9.9	200	10	240
10.9	220	10.5	255
11.9	240	11	269
12.8	260	11.5	283
13.8	280	12	298
14.8	300	13	341

These data are slightly different than that reported by the ADAG study on adults with DM. However, glucose levels comparable to those recorded by ADA were associated with higher HbA1c in our children. The mean increase of 24 h MBG per 1% increase in HbA1c found in our present study (1.1 mmol/L, 20 mg/dL) was lower than that found in either the DCCT study (1.98 mmol/L, 36 mg/dL) (12) or the ADAG study (1.59 mmol/L, 29 mg/dL) (8).

The difference may be attributed to several distinctive characteristics of our population. We included only Arab children with DM-1 with Eastern traditional diet and lifestyle which differ in many aspects compared to the Western traditions. It is well known that racial disparities exist among HbA1c values (13). In addition, there is evidence of wide fluctuations in HbA1c between individuals that are unrelated to glycemic status, suggesting the existence of high and low glycators. High glycators have consistently higher HbA1c than expected for their MBG, whereas low glycators have lower HbA1c than their MBG would suggest (14, 15). In support for this theory, an epidemiologic study found that, when matched for fasting plasma glucose (FPG), African Americans had higher HbA1c than Caucasians (16). This variation in the glycation rate may be attributed to the variations in erythrocyte survival and some yet unknown genetic elements (17-20). Moreover, we used only 5 days glucose data, not all 2-3 months samples, before HbA1c measurement. In support of our data, another study using CGMS over some but not all the 3 months, prior to HbA1c measurement, showed a strong correlation in children with type 1 diabetes, who typically had higher glucose variability (16, 20, 21).

Furthermore, HbA1c levels have been shown to be positively associated with age in nondiabetic populations even after exclusion of subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance test (IGT). Therefore, HbA1C level in children may be lower than in adults with the same MBG (22-25).

Our children with DM-1 had mean GSD=57.6 mg/dl which may increase their risk of developing diabetic complications and may influence on their HbA1c level. CGMS allows better identification of marked fluctuations in blood glucose, and therefore can improve glycemic control.

Because of the relatively small sample size of our study, further studies validating the findings from the present study in children would be required before any implementation of our results could be considered.

Conclusions

Our study showed a linear relationship between A1C and AG values measured by CGMS for 5 days before HbA1c measurement. The AG can be easily calculated using a formula derived from linear regression analysis of HbA1c data obtained in our diabetic children. Fluctuation of blood glucose can evidently affect HbA1c concentration. The proper use of CGMS enables monitoring glucose variability and can help controlling glucose fluctuations. Further studies are needed to determine whether age-specific diagnostic and treatment criteria would be appropriate

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86.
2. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. Diabetol Metab Syndr 2013, 23 (5): 39.
3. Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. Eur J Endocrinol 2012; 166: 567-74.
4. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE.Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care 2002;2 5: 275-8.
5. Makris K, Spanou L, Rambaouni-Antoneli A, Koniari K, Drakopoulos I. Relationship between mean blood glucose and glycated haemoglobin in Type 2 diabetic patients. Diabet Med 2008; 25: 174-178.
6. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; 31: 1473-8.
7. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D,

Heine RJ.A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; 31: 1473-8.
8. American Diabetes Association Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. Diabetes Care 2018; 41(Supplement 1): S13-S27.
9. Klonoff DC. ADAG Study Group Data Links A1C Levels with Empirically Measured Blood Glucose Values - New Treatment Guidelines Will Now be Needed. J Diabetes Sci Technol 2014; 8: 439-43.
10. Herman WH, Ma Y, Uwaifo G, Haffner S, Kahn SE, Horton ES, et al. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007; 30: 2453-7.
11. Yudkin JS, Forrest RD, Jackson CA, Ryle AJ, Davie S, Gould BJ.Unexplained variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. Diabetologia 1990; 33: 208-15.
12. Kilpatrick ES, Maylor PW, Keevil BG. Biological variation of glycated hemoglobin. Implications for diabetes screening and monitoring. Diabetes Care 1998; 21: 261-4.
13. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Ann Intern Med 2011; 154: 303-9.
14. Virtue MA, Furne JK, Nuttall FQ, Levitt MD. Relationship between GHb concentration and erythrocyte survival determined from breath carbon monoxide concentration. Diabetes Care 2004; 27: 931-5.
15. Snieder H, Sawtell PA, Ross L, Walker J, Spector TD, Leslie RD. HbA(1c) levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. Diabetes 2001; 50: 2858-63.
16. Diabetes Research in Children Network (DirecNet) Study Group, Wilson DM, Kollman C. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. Diabetes Care 2008; 31: 381-5.
17. Salardi S, Zucchini S, Santoni R, Ragni L, Gualandi S, Cicognani A, Cacciari E. The glucose area under the profiles obtained with continuous glucose monitoring system relationships with HbA(lc) in pediatric type 1 diabetic patients. Diabetes Care 2002; 25: 1840-4.
18. Pani LN, Korenda L, Meigs JB, Driver C, Chamany S, Fox CS, Sullivan L, D'Agostino RB, Nathan DM. Effect of Aging on A1C Levels in Individuals Without Diabetes: Evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001-2004. Diabetes Care 2008; 31: 1991-6.
19. Vallée Polneau S, Lasserre V, Fonfrède M, Delattre J, Bénazeth S. A different approach to analyzing age-related HbA1c values in non-diabetic subjects. Clin Chem Lab Med 2004; 42: 423-8.
20. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia 2007; 50: 2239-44.
21. Ulf S, Ragnar H, Arne WP, Johnny L. Do high blood glucose peaks contribute to higher HbA1c? Results from repeated continuous glucose measurements in children. World J Pediatr 2008; 4: 215-21.
22. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; 31: 1473-8.
23. Patton SR, Clements MA. Continuous Glucose Monitoring Versus Self-monitoring of Blood Glucose in Children with Type 1 Diabetes- Are there Pros and Cons for Both? US endocrinology 2012; 8(1): 27-9.
24. Satya Krishna SV, Kota SK, Modi KD. Glycemic variability: Clinical implications. Indian J Endocrinol Metab 2013; 17: 611-9.
25. Monnier L, Colette C. Glycemic variability. Should we and can we prevent it? Diabetes Care 2008; 31(Suppl 2): S150-4.

Received: 17 May 2018
Accepted: 31 May 2018
Correspondence:
Ashraf Soliman MD PhD FRCP
Department of Pediatrics, Hamad General Hospital
PO Box 3050, Doha, Qatar
Tel. 0097455983874
E-mail: atsoliman@yahoo.com