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1,5-Anhydroglucitol as a marker of maternal glycaemic control and predictor of neonatal birthweight in pregnancies complicated by type 1 diabetes mellitus

N. Nowak · J. Skupien · K. Cyganek · B. Matejko · M. T. Malecki

Abstract

Aims/hypothesis Most pregnant women with type 1 diabetes mellitus achieve HbA_{1c} targets; however, macrosomia remains prevalent and better pregnancy glycaemic markers are therefore needed. 1,5-Anhydroglucitol (1,5-AG) is a short-term marker of glycaemia, reflecting a period of 1 to 2 weeks. Its excretion rate depends on the renal glucose threshold and thus it is unclear whether it may be used in pregnant type 1 diabetes women. We evaluated 1,5-AG as a glycaemic marker and birthweight predictor in pregnant women with type 1 diabetes, and compared its performance with HbA_{1c}.

Methods 1,5-AG and HbA_{1c} were measured in 82 pregnant women with type 1 diabetes. In addition, 58 continuous glucose monitoring system (CGMS) records were available. Macrosomia was defined as birthweight >90th centile. The data were analysed with Pearson's correlations, and linear and logistic regression models. Receiver operating characteristic (ROC) analysis was used to evaluate third trimester 1,5-AG as a predictor of macrosomia.

Results Unlike HbA_{1c}, 1,5-AG strongly correlated with CGMS indices: the AUC above 7.8 mmol/l ($r=-0.66$; $p<0.001$), average maximum glucose ($r=-0.58$; $p<0.001$) and mean glucose ($r=-0.54$; $p<0.001$). In the third trimester, 1,5-AG was the strongest predictor of macrosomia, with ROC AUC 0.81 (95% CI 0.70, 0.89). In contrast, HbA_{1c} in the third trimester had a ROC AUC of 0.69 (95% CI 0.58, 0.81). The best discrimination was achieved when both markers were used jointly, yielding a ROC AUC of 0.84 (95% CI 0.76, 0.93).

Conclusions/interpretation In pregnant women with type 1 diabetes, 1,5-AG is a better glycaemic marker than HbA_{1c}, as assessed by CGMS. A decreased third trimester 1,5-AG level, either singly or with HbA_{1c}, is a strong predictor of macrosomia.

Keywords 1,5-Anhydroglucitol · Birthweight · Haemoglobin A_{1c} · HbA_{1c} · Pregnancy · Type 1 diabetes mellitus

Abbreviations

1,5-AG	1,5-Anhydroglucitol
CGMS	Continuous glucose monitoring system
NRI	Net reclassification improvement
ROC	Receiver operating characteristic
SMBG	Self-monitoring of blood glucose

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Introduction

Pregnancy complicated by type 1 diabetes mellitus requires tight glycaemic control. Clinical guidelines include HbA_{1c} targets for affected women [1]. A growing number of type 1 diabetic women achieve the recommended HbA_{1c} goal; however, the prevalence of macrosomia remains high [2–4]. This may be because HbA_{1c}, a long-term glycaemic marker, does not reflect short excursions [5]. Moreover, glucose peaks are frequently missed in the conventional self-monitoring of blood glucose (SMBG) [5]. Continuous glucose monitoring systems (CGMS) are still expensive, time-consuming and invasive [6]. An association between levels of fructosamine, a short-term glycaemic marker, and birthweight has been described in pregnant women with type 1 diabetes [7]; however, it is not widely used in clinical practice.

1,5-Anhydroglucitol (1,5-AG) is a monosaccharide, which is sometimes used as a short-term marker of glycaemic excursions, particularly postprandial ones [8]. In contrast to HbA_{1c}, it reflects changes in glycaemic control over the preceding 1 to 2 weeks [9]. Due to its competition with other monosaccharides for reabsorption in the proximal renal tubule, the 1,5-AG excretion rate depends on the renal threshold for glucose [10]. As this threshold is decreased during pregnancy, the clinical value of using 1,5-AG to evaluate glycaemic control in pregnant women with type 1 is currently not established.

We evaluated the association of serum 1,5-AG and HbA_{1c} with CGMS indices, as well as the performance of 1,5-AG and HbA_{1c} levels in predicting macrosomia.

Methods

Patients Between 2008 and 2012 we contacted 98 consecutively presenting pregnant type 1 diabetic women receiving care in the Department of Metabolic Diseases, Krakow, Poland. Of the patients contacted, 92 agreed to participate and 86 completed follow-up until delivery. Since 1,5-AG levels can be altered in chronic renal and liver diseases, we excluded two patients because of hepatic dysfunction; none of the participants had stage 3 or higher chronic kidney disease. In addition, two women who miscarried were not included. Thus, the study group consisted of 82 women whose characteristics are shown in Table 1. The protocol was approved by the Bioethical Committee of the

Table 1 Maternal and neonatal characteristics of the entire study group and subgroups defined by neonatal birthweight

Characteristic	Total (mean, median, SD)			Grouped by birthweight (mean, median, SD)						*p* value
				<90th centile			>90th centile			
	n = 82			*n* = 54			*n* = 28			NA
Maternal										
Maternal age (years)	29.6	29.0	4.5	29.5	29.1	4.6	30.0	30.0	4.4	0.62
Pre-pregnancy BMI (kg/m^2)	23.8	23.2	4.3	23.7	23.0	4.6	24.0	23.5	3.7	0.75
T1DM duration (years)	12.3	12.0	7.3	12.6	11.0	7.6	12.1	12.0	7.2	0.77
Insulin regimen										
MDI (*n*)	2			1			1			NA
CSII (*n*)	80			53			27			NA
MG (mmol/l)										
Second trimester	5.88	5.8	0.83	5.62	5.5	0.58	6.35	6.5	0.97	0.002
Third trimester	5.83	5.8	0.79	5.67	5.5	0.72	6.13	6.0	0.83	0.015
MMG (mmol/l)										
Second trimester	9.34	9.2	1.86	8.56	8.70	1.86	9.87	9.78	1.47	0.001
Third trimester	8.90	8.8	1.70	8.68	8.21	1.98	9.37	9.60	2.06	0.02
HbA_{1c} (%)										
Second trimester	5.5	5.4	0.7	5.3	5.2	0.7	5.8	5.8	0.7	0.001
Third trimester	5.4	5.4	0.7	5.2	5.2	0.6	5.8	5.7	0.7	0.003
HbA_{1c} (mmol/mol)										
Second trimester	37	36	7.2	34	33	7.1	40	40	7.2	NA
Third trimester	36	36	7.1	33	33	6.5	40	39	7.2	NA
1,5-AG (μmol/l)										
Second trimester	29.40	25.71	12.24	33.06	29.17	13.47	23.57	22.65	5.51	0.001
Third trimester	30.18	26.33	11.02	34.29	30.08	11.63	23.54	22.04	5.51	<0.001
Neonatal										
GA at birth (weeks)	38.6	39	1.6	38.6	39	1.7	38.7	39	1.4	0.79
Birthweight (g)	3,501	3,520	647.3	3,148	3,225	463.5	4,205	4,250	280.8	<0.001
Birthweight (centile)	64.6	75	31	45.6	50	25.1	97.3	98	2.4	<0.001

Quantitative traits are presented as mean, median and standard deviation

p values compare the macrosomic and normal weight subgroup and were calculated with Student's *t* test or Mann–Whitney *U* test

CSII, continuous subcutaneous insulin infusion; GA, gestational age; MDI, multiple daily injection; MG, mean glucose; MMG, mean maximum glucose; NA, not applicable; T1DM, type 1 diabetes mellitus

Jagiellonian University. Written informed consent was obtained from all participants.

Clinical measurements In each trimester, the serum 1,5-AG concentration was measured immuno-enzymatically with a kit (1,5-AG ELISA Kit; Cusabio, Wuhan, China). The intra- and inter-assay coefficients of variation were <1.8% and 0.9% to 4.6%, respectively. HbA_{1c} levels were also assessed in each trimester, using high-performance liquid chromatography (Bio-Rad, Strasbourg, France). In 58 women (12, 22 and 24 in the consecutive trimesters), the results of CGMS were analysed for a 7 day period before blood collection for 1,5-AG and HbA_{1c} measurement. Mean glycaemia, its standard deviation, mean maximum glycaemia (defined as the average daily maximum over 7 days), 7 day mean AUC above 7.8 mmol/l (AUC-7.8) and 7 day mean AUC below 3.1 mmol/l (AUC-3.1) were calculated using CGMS software (Medtronic, Minneapolis, MN, USA). Eight-point SMBG profiles were performed daily to calculate mean glucose and mean maximum glucose for the analysis of birthweight and macrosomia in the 82 pregnancies.

Statistical analysis The association of serum 1,5-AG and HbA_{1c} with CGMS indices, as well as the performance of 1,5-AG and HbA_{1c} levels in predicting macrosomia, were examined. The relationship between outcomes (CGMS indices or birthweight) and predictors (1,5-AG or HbA_{1c}) was analysed with Pearson correlations and multiple regression. We controlled for possible confounding by gestational age, pre-pregnancy BMI or maternal age. Skewed data were log-transformed. Logistic regression, receiver operating characteristic (ROC) analysis and continuous net reclassification improvement (NRI) [11] were used to evaluate 1,5-AG and HbA_{1c} as predictors of macrosomia, defined as a neonatal birthweight >90th percentile (sex-specific) in the Polish population. Statistical calculations were performed with MedCalc 9.3.8 (MedCalc Software, Ostend, Belgium) and SAS 9.3 (SAS Institute, Cary, NC, USA). Values of $p<0.05$ were considered significant.

Results

Glycemic control The group of type 1 diabetic women examined by us had excellent glycaemic control, as defined by HbA_{1c} targets. Mean HbA_{1c} levels were 5.8±0.9%, 5.5±0.7% and 5.4±0.7% (40±10, 37±7 and 36±7 mmol/mol) in first, second and third trimesters respectively. There was no difference in mean 1,5-AG levels between consecutive pregnancy trimesters (30.0± 11.0, 29.4±12.2, 30.0±11.0 μmol/l; 4.9±1.8, 4.8±2 and 4.9±1.8 μg/ml; $p=0.4$, respectively).

Association of HbA_{1c} and 1,5-AG with CGMS To evaluate 1,5-AG and HbA_{1c} as markers of glucose levels, we used CGMS measurements from 56 women at various gestational ages. Interestingly, there was no correlation between 1,5-AG and HbA_{1c} ($r=-0.07$; $p=0.57$). 1,5-AG correlated strongly with CGMS-based mean glucose ($r=-0.54$; $p<0.001$), and with a metric of glucose variability (amplitude)—standard deviation ($r=0.60$; $p<0.001$). In addition, 1,5-AG correlated with two metrics of hyperglycaemia: average maximum glucose ($r=-0.58$; $p<0.001$) and AUC-7.8 ($r=-0.66$; $p<0.001$). It did not correlate ($r=0.05$, $p=0.70$) with hypoglycaemia (AUC-3.1). HbA_{1c} was weakly correlated with mean glucose ($r=0.34$; $p=0.01$), but not with standard deviation ($r=0.17$; $p= 0.23$), mean maximum glucose ($r=0.2$; $p=0.14$), AUC-7.8 ($r= 0.22$; $p=0.10$) and AUC-3.1 ($r=-0.23$; $p=0.10$). The pattern of correlations was not affected when the analysis was restricted to a particular trimester. In regression models, in which CGMS indices (except AUC-3.1) were used as dependent variables, 1,5-AG was always statistically independent of HbA_{1c} ($p<0.001$ in each model).

Predicting macrosomia with 1,5-AG and HbA_{1c} We subsequently evaluated 1,5-AG in 82 women as a risk marker of clinical outcome, birthweight and macrosomia. In 28 (34%) pregnancies, macrosomia was diagnosed. Interestingly, in 22 mothers of macrosomic newborns (80% of macrosomia cases) third trimester HbA_{1c} was <6.0% (42 mmol/mol). The mean second and third trimester 1,5-AG concentrations (Table 1) were significantly lower in mothers of macrosomic babies ($p=0.001$ and $p<0.001$ for the second and third trimester, respectively). The correlation coefficient of 1,5-AG levels with birthweight was $r=-0.44$ ($p<0.001$) for the second and $r= -0.58$ ($p<0.001$) for the third trimester. The corresponding coefficients for second and third trimester HbA_{1c} levels were 0.29 ($p=0.014$) and 0.32 ($p=0.005$), respectively. In the multivariate linear regression model, the 1,5-AG level, either in the second or third trimester, was associated with birthweight independently ($p<0.001$) of HbA_{1c}, after adjusting for confounders.

The third trimester 1,5-AG value, the strongest predictor of birthweight, was evaluated in logistic regression as a risk marker of macrosomia. The relative odds of macrosomia per 1 μg/ml (6.1 μmol/l) decrease in 1,5-AG was 3.0 (95% CI 1.6, 5.8; $p=0.001$). In ROC analysis the AUC reached 0.81 (95% CI 0.70, 0.89). The optimum sensitivity, specificity, and corresponding positive and negative predictive values were 96.3%, 56%, 55% and 96.6%, respectively at 4.76 μg/ml (29.0 μmol/l) as cut-off value for 1,5-AG (Fig. 1). Additionally, the AUC of 1,5-AG in the second trimester was 0.75 (95% CI 0.64, 0.86). In comparison, the AUC of HbA_{1c} in the third and second trimester was 0.69 (95% CI 0.58, 0.81) and 0.71 (95% CI 0.59, 0.83), respectively. The difference between the AUC of 1,5-AG and HbA_{1c} (0.81 vs 0.69) was not statistically significant ($p=0.15$); however, another

Fig. 1 ROC curve analysis for third trimester maternal 1,5-AG. (**a**) ROC curve illustrating the accuracy of 1,5-AG in predicting neonate macrosomia. Circle, optimum value; diagonal dotted line, the null value of ROC curve. (**b**) Sensitivity (black) and specificity (grey) plotted against cut-off value of 1,5-AG concentration
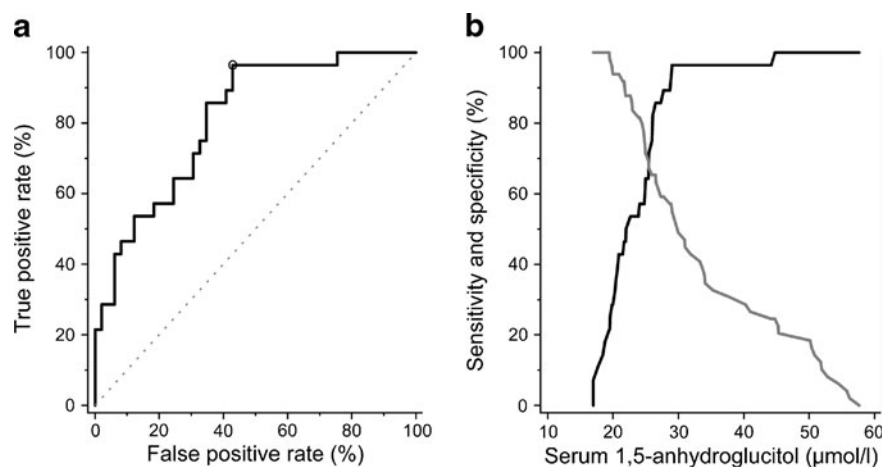
discrimination measure, NRI [11], was 0.49 (95% CI 0.05, 0.93; $p=0.028$) in favour of 1,5-AG.

Since HbA_{1c} and 1,5-AG are independently associated with birthweight, we used the third trimester markers 1,5-AG in combination with HbA_{1c} to predict macrosomia. This model had a substantially improved AUC of 0.84 (95% CI 0.76, 0.93), which was significantly better than HbA_{1c} alone ($p=0.009$). The NRI was 0.94 (95% CI 0.56, 1.31; $p<0.001$). The addition of second trimester markers, maternal age and BMI did not alter the results and did not significantly improve prediction. Using the predictive score derived from the model variables $1.2 \times (HbA_{1c}\ [\%]) - (1,5\text{-AG}\ [\mu g/ml])$ or ($HbA_{1c}\ [mmol/mol]) - 1.5 \times (1,5\text{-AG}\ [\mu mol/l])$, we obtained optimum sensitivity, specificity, and positive and negative predictive values of 85.7%, 71.4%, 63.2% and 89.7%, respectively, where score values ≥ 2.14 (or ≥ -4.13, when molar concentrations are used) indicated risk of macrosomia with relative odds of 2.8 (95% CI 1.6, 4.8; $p<0.001$).

Discussion

In our study of pregnant women with type 1 diabetes mellitus, levels of 1,5-AG, a short-term glycaemic marker that, unlike HbA_{1c}, captures episodes of hyperglycaemia, were strongly correlated with indices derived from CGMS. The observed negative correlations between 1,5-AG levels and CGMS metrics are in agreement with earlier studies involving non-pregnant diabetic participants [8]. It has also been previously shown that HbA_{1c} levels did not correlate well with maternal glucose profiles measured with CGMS [5]. This seems to explain the high rate of adverse pregnancy outcomes observed earlier [2–4] and in this study, despite patients achieving the recommended HbA_{1c} values.

This finding could be of clinical importance, as we have shown for the first time that 1,5-AG provides insight into short-term glycaemic control in pregnant women with type 1 diabetes. Its use may improve the assessment of whether insulin dosage modifications are necessary, eventually helping improve pregnancy outcomes. Currently, patients with type 1 diabetes are mainly monitored by daily SMBG in combination with HbA_{1c}. 1,5-AG, which responds rapidly to changes in glucose profile, may facilitate treatment adjustments, providing an accurate, rapid, possibly cost-effective and practical additional or even alternative tool to HbA_{1c}, and one that probably would also be more reliable and objective than SMBG.

Another new finding was that third trimester 1,5-AG levels appeared to be a strong predictor of macrosomia and, as indicated by AUC values in ROC analysis, performed better than HbA_{1c}. It should be noted that most mothers of macrosomic babies met HbA_{1c}-based criteria of glycaemic control. The high risk of macrosomia in such patients may be explained by glucose excursions that were undetected with HbA_{1c}, but were reflected in their 1,5-AG levels. Indeed, 1,5-AG was strongly associated with CGMS AUC-7.8, standard deviation and average maximum glycaemia. 1,5-AG could therefore be a particularly suitable marker in patients achieving HbA_{1c} targets. Although 1,5-AG singly was superior to HbA_{1c} in predicting risk of macrosomia, even better results were achieved when both markers were used jointly. Since 1,5-AG and HbA_{1c} were uncorrelated, the best discriminative accuracy was achieved when information from both these markers was combined in the proposed risk index. A possible shortcoming of our study is that two short-term measures, 1,5-AG and CGMS, were analysed together with a long-term measure, HbA_{1c}. In addition, the difference in the prediction power of macrosomia risk between 1,5-AG and HbA_{1c} was rather moderate. Future clinical

studies targeting HbA$_{1c}$ and 1,5-AG therapeutic goals in pregnant women with type 1 diabetes would be of tremendous interest.

In spite of earlier concerns [10] that the decreased renal threshold for glucose in pregnancy might lower the 1,5-AG level and potentially decrease its ability to differentiate well- and poorly controlled diabetes, 1,5-AG in our study appeared to be a very good marker of glycaemia in pregnant women with type 1 diabetes. During pregnancy, our patients achieved excellent glycaemic targets, which would have acted in the opposite direction to that of an altered renal threshold, i.e. by increasing the 1,5-AG level. Eventually, 1,5-AG remained very sensitive to hyperglycaemia. Its performance in pregnant women with other types of diabetes, who may differ not only by the degree of metabolic control but also in terms of glycaemic fluctuations, requires further evaluation.

In summary, 1,5-AG performs better than HbA$_{1c}$ as a tool for monitoring the glucose profile in pregnancies complicated by type 1 diabetes. Its decreased third trimester level is a very valuable predictor of macrosomia, particularly considered together with HbA$_{1c}$. The determination of 1,5-AG should be considered for clinical use in type 1 diabetic pregnancies.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement NN and MTM were responsible for study design and protocol development; JS and NN carried out data analysis; NN, KC, BM and MTM were responsible for the acquisition and interpretation of data; NN, JS and MTM drafted the article; KC and BM revised the manuscript for important intellectual content; all authors gave final approval of the version to be published; MTM was the project coordinator.

References

1. American Diabetes Association. Standards of medical care in diabetes—2012. Diabetes Care 35 Suppl 1: S11–S63
2. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH (2002) Macrosomia despite good glycaemic control in type I diabetic pregnancy; results of a nationwide study in the Netherlands. Diabetologia 45:1484–1489
3. Kerssen A, de Valk HW, Visser GH (2007) Increased second trimester maternal glucose levels are related to extremely large-for-gestational-age infants in women with type 1 diabetes. Diabetes Care 30:1069–1074
4. Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M (2003) Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. Obstet Gynecol 101:633–638
5. Kerssen A, de Valk HW, Visser GH (2006) Do HbA1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus? Diabetologia 49:25–28
6. Hermanides J, Phillip M, DeVries JH (2011) Current application of continuous glucose monitoring in the treatment of diabetes. Pros Cons Diabetes Care 34(Suppl 2):197–201
7. Page RC, Kirk BA, Fay T, Wilcox M, Hosking DJ, Jeffcoate WJ (1996) Is macrosomia associated with poor glycaemic control in diabetic pregnancy? Diabet Med 13:170–174
8. McGill JB, Cole TG, Nowatzke W et al (2004) Circulating 1,5-anhydroglucitol levels in adult patients with diabetes reflect longitudinal changes of glycemia: a U.S. trial of the GlycoMark assay. Diabetes Care 8:1859–1865
9. Dungan KM, Buse JB, Largay J et al (2006) 1,5-Anhydroglucitol and postprandial hyperglycemia as measured by Continuous Glucose Monitoring System in moderately controlled patients with diabetes. Diabetes Care 29:1214–1219
10. Kilpatrick ES, Keevil BG, Richmond KL, Newland P, Addison GM (1999) Plasma 1,5-anhydroglucitol concentrations are influenced by variations in the renal threshold for glucose. Diabet Med 16:496–499
11. Pencina MJ, D'Agostino RB, Steyerberg EW (2011) Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Statist Med 30:11–21