Correlation between self-monitored mean blood glucose and average plasma glucose estimated from glycated haemoglobin in patients attending the diabetes clinic at Dr George Mukhari Academic Hospital, Pretoria, South Africa

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Background. Glycated haemoglobin (HbA1c) has been used for decades as a measure of chronic glycaemia. A simple linear relationship between HbA1c values and mean blood glucose (MBG) has been identified and led to conversion of HbA1c values into estimated average glucose (eAG) levels, following the findings of the A1c-Derived Average Glucose (ADAG) Study Group. The intention was to help patients with diabetes mellitus (DM) understand their glycaemic control better, as eAG is reported in the same units as self-monitored glucose levels. However, factors other than glycaemia have been found to affect the relationship between HbA1c and MBG.

Objectives. To: (*i*) determine the relationship between self-monitored MBG levels and HbA1c values; and (*ii*) evaluate the correlation between MBG levels and eAG levels calculated from HbA1c values using the regression equation derived from the ADAG Study Group in black South African patients with DM.

Methods. This was a prospective observational study of 96 diabetic patients. MBG levels were calculated using glucose measurements downloaded from the glucose meters for the previous 90 days (3 months). High-performance liquid chromatography was used for measurement of HbA1c values, collected at the end of 3 months. eAG was calculated using the regression equation from the ADAG Study Group, as follows: eAG (mmol/L) = 1.5944 × HbA1c (NGSP, %) − 2.594.

Results. A positive correlation was found between MBG and HbA1c in all participants (R^2=0.69, p<0.0001). There was a wide range of MBG levels for any given HbA1c value. Clinically significant differences between MBG and eAG were found, with a ≥10% difference in 65.6% of the participants. eAG overestimated MBG in ~71.8% of the study population, with an overestimation of ≥1.6 mmol/L (28.7 mg/dL, equivalent to a 1% change in HbA1c value) in ~50% of the total study population.

Conclusions. Our findings showed an imperfect relationship between MBG levels and HbA1c values. eAG significantly overestimated MBG, and this disagreement may cause confusion among both patients and clinicians. The risk of hypoglycaemic episodes may also increase if HbA1c and eAG alone are used to intensify therapy. We recommend that the use of eAG should be validated prior to implementation in clinical practice. It would be ideal to evaluate the relationship between average glucose and HbA1c in each individual patient in order to provide more personalised diabetes care.

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The management of diabetes mellitus (DM) demands accurate assessment of glycaemic control to determine the efficacy of treatment. For decades, glycated haemoglobin (HbA1c) has been a surrogate marker to monitor the control of glycaemia and predict the risk of microvascular complications in patients with DM.[1,2] The Diabetes Control and Complications Trial (DCCT) showed that intensive glycaemic control significantly reduced the risk of long-term microvascular complications for patients with type 1 DM.[3] Similar findings were subsequently reported for patients with type 2 DM.[4] HbA1c values reflect mean blood glucose (MBG) during the preceding 2 - 3 months, making it a good marker for long-term assessment of glycaemic control.[4,5]

The American Diabetic Association (ADA) recommends self-monitoring of blood glucose and HbA1c as the two techniques to assess glycaemic control. Self-monitoring of blood glucose forms an important component of glucose monitoring in patients with DM, especially those taking insulin therapy, for adjustment of therapy and to prevent hypoglycaemic episodes.[5]

Patient participation is critical in diabetes care, and most patients are familiar with glucose levels and may find it difficult to relate HbA1c values to glucose levels. This problem has led to the derivation of a regression equation for calculating the estimated average glucose (eAG) from the HbA1c value, following the demonstration of a linear relationship between HbA1c values and MBG levels.[6] However, to date numerous regression equations have been formulated by many studies,[7] with published data showing substantial variation in individual MBG for a given HbA1c value.[8,9] Most commonly used is Nathan's regression equation, derived using data from the A1c-Derived Average Glucose (ADAG) Study Group,[6] previously adopted by the ADA[10] and now implemented in most laboratories. It was hoped that patients would understand the changes in their HbA1c better if they could relate them to eAG.

While eAG may improve patients' participation in their diabetic control, the mean value determined from daily capillary glucose monitoring may or may not correlate with the eAG calculated from the HbA1c value. If these two values differ, patients are likely to become confused about their glycaemic status. This possibility should be considered before providing the patient with eAG levels at their follow-up visit, to avoid confusion.

We determined the relationship between self-monitored MBG levels and HbA1c values and the correlation between MBG and HbA1c-derived eAG using the equation from the ADAG Study Group.

Methods
Participants
This observational study was conducted in the diabetes clinic at Dr George Mukhari Academic Hospital, Pretoria, South Africa. Data were collected between October 2017 and January 2018. One hundred and thirty-six patients with DM were initially enrolled in the study. Pregnant women and patients who had conditions such as anaemia, reticulocytosis, chronic renal or liver failure, blood loss and/or transfusion, haemoglobinopathies, or iron, vitamin B_{12} and folate deficiencies, as well as those on high-dose vitamin C, steroids or erythropoietin therapy, were excluded from the study.

We excluded 40 patients from the study owing to a history of chronic kidney disease with associated anaemia of chronic disease (n=32) and anaemia due to iron and vitamin B_{12} deficiencies (n=8). The remaining 96 patients were evaluated. The study was approved by the institutional ethical committee (ref. no. MREC/P/241/2014), and informed consent was obtained from all participants.

Glycated haemoglobin assay
Blood for HbA1c testing was collected in ethylenediaminetetra-acetic acid specimen tubes on the day of the clinic visit. HbA1c values were measured by ion-exchange high-performance liquid chromatography using the VARIANT II TURBO system (Bio-Rad Laboratories, USA). The analytical coefficient of variation (CV) of the assay for the duration of the study was 0.8% in National Glycohemoglobin Standardization Program (NGSP) units and 1.2% in SI units. This method is certified by the NGSP and is traceable to the DCCT.

Mean blood glucose determination
Self-monitoring capillary glucose measurements were done using the On Call Plus device (On Call Plus Blood Glucose Monitoring System, USA). The day-to-day CV claimed by the manufacturer ranged from 3.3% to 5.0%, assessed using glucose levels ranging from 1.7 mmol/L to 28 mmol/L. Most participants measured their capillary blood glucose twice a day, in the morning before meals and at bedtime. All participants who tested at least once a day were included in the study. Of patients who did fewer glucose tests, only those who tested at least once a day in the month (30 days) preceding their clinic visit were included. A strong correlation has been reported between MBG levels (measured during the preceding month) and HbA1c values.[2] Glucose results were downloaded from the device on the day of the clinic visit. The MBG levels were determined by calculating the average value of all the glucose measurements downloaded from the glucose device for the previous 90 days (3 months).

Estimated average glucose calculation
The eAG was calculated from the HbA1c (%) results using the equation derived from the ADAG Study Group: eAG (mmol/L) = 1.5944 × HbA1c (NGSP, %) – 2.594, (R^2=0.84, p<0.0001).[6]

Statistical analysis
All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 11.0 for Windows; IBM, USA). The Kolmogorov-Smirnov test was used to evaluate the distribution of the variables. The linear regression model was applied to estimate the relationship between HbA1c and MBG, and Spearman's test was used to assess the correlation between the two parameters. A two-tailed p-value <0.05 was accepted as significant.

The influence of age, gender, type of DM, history of smoking, alcohol use, insulin therapy, hypertension, socioeconomic status and level of education on the relationship between MBG and HbA1c was examined by comparing the slope (MBG v. HbA1c) among the individual subgroups using Fisher Z-transformation (z-observations). Predicted MBG was calculated from HbA1c values based on the regression analysis between MBG and HbA1c.

Agreement between MBG and eAG levels was assessed using Bland-Altman analysis. The limits of agreement (LOA) were set at the internationally accepted maximum error limit of ±10%.[11] The absolute and percentage differences between eAG and MBG were also calculated for each individual to determine their clinical significance.

Results
Characteristics of the study cohort
The study group consisted of 96 black diabetic patients with a median age of 62 years (range 14 - 88 years), of whom 88.5% had type 2 DM and 64.6% were female. The number of capillary glucose measurements ranged from 45 to 297 per participant, with a total of 12 370 glucose tests during the 3-month period. The frequency of glucose testing per day, prior to the measurement of HbA1c at day 90, is shown in Fig. 1. Baseline characteristics of the whole cohort are shown in Table 1. The distributions of age, HbA1c, MBG and eAG were abnormal (p<0.05).

Correlation between MBG and HbA1c
A positive correlation was found between MBG and HbA1c in all participants (R^2=0.69; p<0.0001) (Fig. 2). The slope of MBG levels v. HbA1c values was 1.20 mmol/L per 1% HbA1c with an intercept of 0.49 mmol/L, and the Spearman's correlation coefficient (r) was 0.83 (Fig. 2). Factors such as age, gender, smoking status, type of DM, history of alcohol use and insulin therapy as well as socioeconomic status and patient's level of education did not meaningfully affect the slope for MBG v. HbA1c.
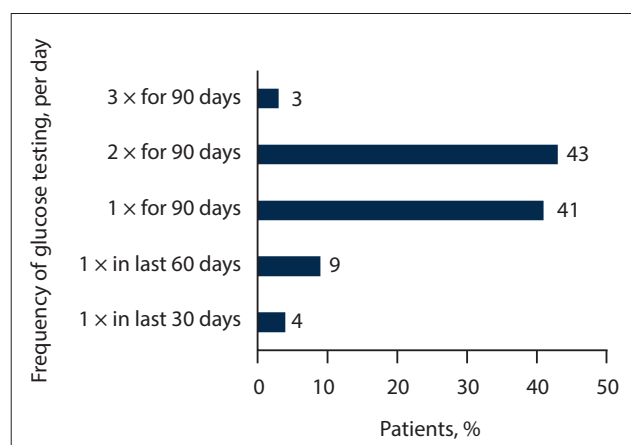

Fig. 1. Frequency of capillary glucose testing per day in the whole study population.

Table 1. Baseline characteristics

Parameters	Total population	Type 1 DM	Type 2 DM
n (%)	96 (100)	11 (11.5)	85 (88.5)
Age (years), median (IQR)/mean (SD)	62.0 (50.3 - 67.8)	19.5 (4.8)	63 (57.5 - 69)
Sex female, *n* (%)	62 (64.6)	8 (72.7)	54 (63.5)
Hb (g/dL), mean (SD)	13.8 (0.02)	13.8 (0.02)	13.7 (0.03)
HbA1c (%), median (IQR)/mean (SD)	8 (6.9 - 11.4)	8.8 (2.6)	7.9 (6.9 - 10.2)
HbA1c (mmol/mol), median (IQR)/mean (SD)	64 (52 - 101)	72.2 (28.6)	63 (52 - 88)
eAG (mmol/L), median (IQR)/mean (SD)	10.2 (8.4 - 15.6)	11.4 (4.2)	10 (8.4 - 13.7)
MBG (mmol/L), median (IQR)/mean (SD)	9.2 (7.3 - 9.2)	10.1 (4.0)	9 (7.2 - 12)
Smoker, *n* (%)	6 (6.3)	0	6 (6.3)
Alcohol use, *n* (%)	10 (10.4)	0	10 (10.4)
Insulin therapy, *n* (%)	75 (78.1)	11 (100)	64 (75.3)

DM = diabetes mellitus; IQR = interquartile range; SD = standard deviation; Hb = haemoglobin; HbA1c = glycated haemoglobin; eAG = estimated average glucose (mmol/L) = 1.5944 × HbA1c (NGSP, %) – 2.594; MBG = mean blood glucose; NGSP = National Glycohemoglobin Standardization Program.

Predicted MBG levels calculated from HbA1c values based on the regression equation from the present study are shown in Table 2, in both conventional and SI units with 95% confidence intervals (CIs).

Agreement between MBG and eAG

The characteristics of the present study compared with the ADAG Study Group are shown in Table 3. The slope and the intercept of the regression equation correlating MBG to HbA1c in our study were lower than those found by the ADAG Study Group.

A Bland-Altman plot was used to assess the agreement between eAG and MBG (Fig. 3). The whole-group average of MBG and eAG was depicted on the *x*-axis, with the percentage difference between the two parameters on the *y*-axis. The percentage difference was determined by dividing the absolute value of the difference between eAG and MBG (eAG – MBG) by the average of the two parameters [(eAG + MBG)/2)], multiplied by 100. The LOA were set at the internationally accepted maximum error limit of ±10%.

Poor agreement was observed between MBG and eAG. Most results (65.6%) fell outside the limits of agreement (Fig. 3). eAG overestimated MBG in 74.0% of participants, and underestimated MBG in 24.2%. The overestimation and under-estimation of MBG was clinically significant (percentage difference ≥10%) in 56.3% and 9.4%, respectively. Table 4 shows the total number of participants with a clinically significant difference between MBG and eAG.

The slope of the regression equation in the ADAG study was 1.6 mmol/L (28.7 mg/dL) of glucose for every 1% change in HbA1c, so a difference between MBG and
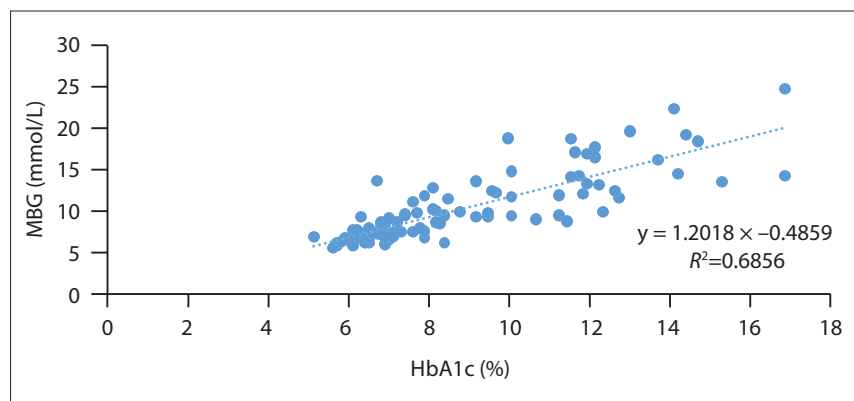

Fig. 2. MBG v. HbA1c. MBG measured by glucose meter over a period of 3 months (90 days), HbA1c measured at the end of month 3. The regression line was calculated using least squares. (MBG = mean blood glucose; HbA1c = glycated haemoglobin.)

$$y = 1.2018 \times -0.4859$$
$$R^2 = 0.6856$$

Table 2. Predicted MBG for HbA1c values

HbA1c (%)	MBG	
	mmol/L, mean (95% CI)*	mg/dL, mean (95% CI)†
5	5.5 (3.1 - 7.9)	99 (56 - 143)
6	6.7 (4.2 - 9.3)	121 (75 - 167)
7	7.9 (5.2 - 10.7)	142 (93 - 192)
8	9.1 (6.2 - 12.0)	164 (112 - 216)
9	10.3 (7.3 - 13.4)	186 (130 - 241)
10	11.5 (8.3 - 14.8)	207 (149 - 266)
11	12.7 (9.3 - 16.1)	229 (168 - 290)
12	13.9 (10.4 - 17.5)	250 (186 - 315)

MBG = mean blood glucose; HbA1c = glycated haemoglobin; CI = confidence interval.
*Linear regression: MBG (mmol/L) = 1.2 × HbA1c – 0.5.
†Linear regression: MBG (mg/dL) = 21.6 × HbA1c – 8.8.

eAG of 1.6 mmol/L (28 mg/dL) would be equivalent to a difference of 1% HbA1c. A difference of ≥0.5% HbA1c represents a statistically significant change in glycaemic control. In this study, 71.8% of participants had a difference of ≥0.5% HbA1c, which was represented by an absolute difference of ≥0.8 mmol/L (14.4 mg/dL) between eAG and MBG (Table 5).

Discussion

Our study supports the notion of a linear relationship between HbA1c values and MBG, but the correlation was poor ($R^2 = 0.69$) compared with other studies that showed a strong relationship – Nathan *et al.*[6] ($R^2 = 0.84$) and Makris *et al.*[12] ($R^2 = 0.86$). The slope of the regression equation in our study was 1.2 mmol/L (21.7 mg/dL) glucose

Table 3. Characteristics of the present study v. the ADAG Study Group[6]

	Subjects (N)	Ethnic group	HbA1c range (%), mean (SD)	Method	Curve fit (R²)	Slope (mmol/L (mg/dL))	Intercept (mmol/L (mg/dL))
Present study	96	100% black African	9.0 (2.8)	Infrequent discrete testing	Linear (0.69)	1.20 (21.6)	0.49 (8.8)
ADAG Study Group	507	83% white, 8% African American, 8% Hispanic, 2% other	6.8 (1.3)	Intermittent CGM	Linear (0.84)	1.59 (28.7)	2.59 (46.7)

ADAG = A1c-Derived Average Glucose; CGM = continuous glucose monitoring.
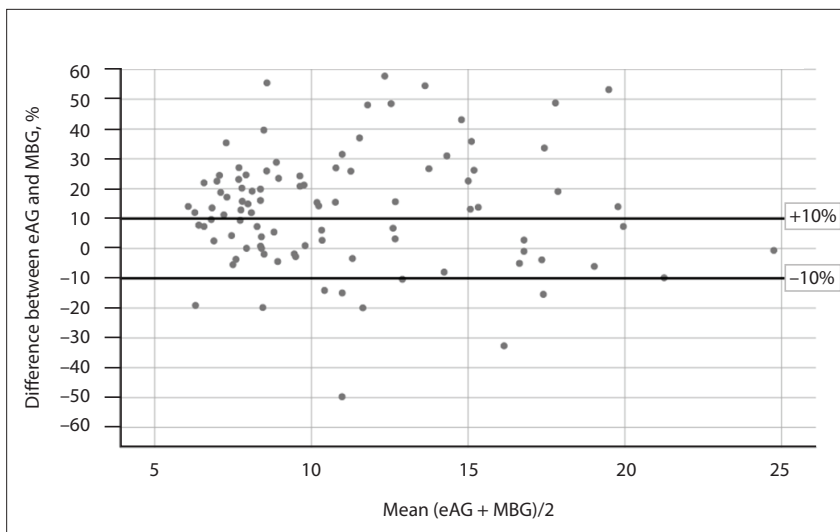
Fig. 3. Bland-Altman plot of the whole group. (eAG = estimated average glucose (mmol/L) = 1.5944 × HbA1c (NGSP, %) – 2.594); MBG = mean blood glucose; NGSP = National Glycohemoglobin Standardization Program.)

for every 1% change in HbA1c. This value is similar to the results of other studies that used continuous glucose monitoring (CGM) devices,[8,9] but is lower than the value reported by Rofhling *et al.*[13] in a study analysing data from the DCCT (slope of 36 mg/dL (2 mmol/L)) and by the ADAG Study Group[6] (slope of 28.7 mg/dL (1.6 mmol/L)). This means that in our study population, smaller changes in glucose concentrations translate to large differences in HbA1c values.

There was a wide range of MBG levels for any given HbA1c value in the present study. For example, the MBG ranged from 6.0 to 8.2 mmol/L (107.9 - 138.3 mg/dL) for an HbA1c of 7% (*n*=7) (Fig. 2), suggesting an imperfect relationship between MBG and HbA1c. Factors such as age, gender, smoking status, type of DM, history of alcohol use and insulin therapy, as well as socioeconomic status and patient level of education, did not meaningfully affect the slope for MBG v. HbA1c.

An imperfect relationship between MBG and HbA1c is also demonstrated by the

predicted MBG levels for HbA1c values derived from the regression equation (MBG v. HbA1c of the total study population), which showed a wide range in predicted MBG levels for any given HbA1c value (Table 2). The predicted MBG levels also showed an overlap between HbA1c values. For example, at an HbA1c value of 7%, the predicted MBG was 7.9 mmol/L with a 95% CI ranging from 5.2 to 10.7 mmol/L, which overlaps with the 95% CI of the MBG at HbA1c of 8% (6.2 - 12.0 mmol/L) (Table 2).

The poor correlation observed in our study could be due to inaccurate calculation of the MBG, either from infrequent measurements of blood glucose or portable meter inaccuracies. The majority of the study participants were elderly (55% of the study population were aged >60 years), and they may have struggled with the capillary glucose measurements or used improper measurement techniques, even though they received prior training. However, other studies that incorporated the use of CGM, which offers the most accurate assessment of glycaemia, also reported a poor correlation

between HbA1c and MBG, supporting the notion that the discrepancy could be due to biological variation in erythrocyte survival or glycation rates.[8,9,13-15]

Numerous authors have hypothesised that the rate of glycation is not constant, and that even at the same MBG the glycation rate may differ between individuals, as some patients are high glycators while others are low glycators. Even if they have the same MBG, the high glycators will have much higher HbA1c than the low glycators.[15] Racial and ethnic differences in the relationship between HbA1c levels and average glycaemia have also been reported, and non-glycaemic factors affecting haemoglobin glycation, differences in red cell survival, and the balance of glucose between the extracellular and intracellular red blood cell environment have been postulated as probable contributing factors.[16-20]

The second objective of our study was to evaluate the application of the HbA1c-derived eAG (ADAG equation) in our study population. Disagreement between MBG and eAG was observed (Fig. 3). We found clinically significant differences between MBG and eAG (Table 4), with MBG significantly overestimated in 56.3% of the total number of participants and underestimated in 9.4%. Further analysis showed that eAG overestimated MBG by ≥0.8 mmol/L (14.4 mg/dL, equivalent to a 0.5% change in HbA1c value) in ~71.8% of all participants (Table 5). A 0.5% change in HbA1c represents a statistically significant change in glycaemic control.[21,22] If HbA1c and eAG alone are used to adjust anti-glycaemic therapy, there would therefore be an increased risk of hypoglycaemic episodes.

The differences in the study designs between the ADAG study and the present study may have attributed to the observed poor correlation between MBG and eAG. Firstly, 83% of the ADAG study participants were white and only 8% were African American, whereas only black South Africans were included in our study. The

Table 4. Number of participants with clinically significant difference between eAG and MBG

Difference between eAG and MBG, %	Participants, n (%)
≥10	26 (27.1)
≥20	37 (38.5)

eAG = estimated average glucose (mmol/L) = 1.5944 × HbA1c (NGSP, %) – 2.594; MBG = mean blood glucose; NGSP = National Glycohemoglobin Standardization Program.

Table 5. Number of patients with absolute difference between eAG and MBG

Absolute difference (eAG – MBG)	Difference in HbA1c (%)	Patients, n (%)
≥0.8 mmol/L (14.4 mg/dL)	0.5	21 (21.9)
≥1.6 mmol/L (28.7 mg/dL)	1	22 (22.9)
≥2.4 mmol/L (43.1 mg/dL)	1.5	26 (27.1)

eAG = estimated average glucose (mmol/L) = 1.5944 × HbA1c (NGSP, %) – 2.594; MBG = mean blood glucose; NGSP = National Glycohemoglobin Standardization Program.

findings of the ADAG study suggested a different slope and intercept in the regression line (p=0.07) for African Americans, indicating that they may have slightly lower MBG levels for a given value of HbA1c. These findings are indeed in keeping with the overestimation of MBG by eAG (derived from the ADAG regression equation) observed in our study. The slope and intercept of the regression line found in our study are lower than those in the ADAG study (Table 3). Racial and ethnic variations in HbA1c have been reported.[16,20]

Secondly, the ADAG study population included both type 1 and type 2 diabetic patients as well as non-diabetic participants. In contrast, our study population was composed of only diabetic patients (type 1 and type 2 DM). Lastly, only patients with stable glycaemia participated in the ADAG study, while there were no selection criteria in respect of glycaemic stability in our study group. As a result, the ADAG study-derived regression equation may be applicable only to patients with stable glycaemia.

The ADAG Study Group has recommended translation of HbA1c values to eAG levels in order to enable patients to understand their glycaemic status better, as it is reported in the same units as values obtained from patient self-monitoring.[6] Many laboratories today are reporting HbA1c results with eAG levels. In order to use eAG to reliably guide the management of diabetic patients, a fairly close agreement should exist between eAG and MBG in most patients. Our findings showed that eAG significantly overestimated MBG, and if HbA1c and eAG alone are used by clinicians to monitor glycaemic control and adjust therapy, there may therefore be an increased risk of hypoglycaemic episodes. The disagreement between MBG and eAG may also cause confusion in patients who self-monitor their MBG.

Study limitations

Limitations of this study include the use of glucose meters (discrete method) to determine MBG levels, which may have influenced the accuracy of MBG levels as a result of infrequent glucose measurements. The inclusion of participants who had a limited number of glucose tests (<1 test per day) may have also affected the accuracy of MBG levels for those participants. However, when these patients were excluded from analysis, there was no statistically significant difference in the slope of the regression line between MBG and HbA1c when data for the remaining participants were analysed (1.2 v. 1.1). Type 1 DM patients were under-represented in our study (11.5 %), so our findings may not be applicable to this group.

Conclusions

Our study has shown an imperfect relationship between MBG and HbA1c. Our findings disagree with the conclusions of the ADAG Study Group that a calculated mean glucose derived from HbA1c is clinically equivalent to self-monitored MBG. Our findings further suggest that in our population, eAG overestimated MBG in most participants. This disagreement may lead to confusion on the part of both patients and clinicians. The risk of hypoglycaemic episodes may also increase if HbA1c and eAG alone are used to intensify therapy. We recommend that the use of eAG should be validated prior to implementation in clinical practice.

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