Do high blood glucose peaks contribute to higher HbA_{1c}? Results from repeated continuous glucose measurements in children

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Background: **HbA_{1c} levels are influenced by the glycemic control of previous 2-3 months. Sometimes patients have surprisingly low HbA_{1c} in spite of many correctly measured high blood glucose values, which is difficult to explain. As glucose sensors give an objective picture based on glucose readings several times per minute over 24 hours, we used the area under the curve (AUC) of such subcutaneous glucose profiles to evaluate their relationship with HbA_{1c}.**

Methods: **Thirty-two patients were randomized into two study arms, one open and the other blinded. Both arms had 8 pump users and 8 patients with multiple daily injections (MDI). After three months the two arms crossed over. Both study arms wore a continuous glucose monitoring system (CGMS) for 3 days every 2 weeks. HbA_{1c} was determined before and after each 3-month study period.**

Results: **There was no relationship between HbA_{1c} and s.c. glucose AUC or between HbA_{1c} and the number of peaks >15.0 mmol/L when all CGMS profiles during the 6 months were taken together. Children on MDI showed a positive relationship between HbA_{1c} and AUC (P<0.01) as well as the number of peaks (P<0.01). Children with a negative relationship between HbA_{1c} and AUC generally had fewer fluctuations in blood glucose values, whereas children with a positive relationship had wide fluctuations.**

Conclusions: **Although there was no relationship between s.c. glucose AUC and HbA_{1c}, the results indicate that wide blood glucose fluctuations may be related to high HbA_{1c} values. Therefore, complications and therapeutic interventions should aim at reducing such fluctuations.**

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Key words: **blood glucose;**
diabetes;
HbA_{1c};
multiple daily injections

Introduction

Since the Diabetes Control and Complication Study presented the final decisive answer that good metabolic control can prevent vascular complications,[1] no one has disputed the importance of good metabolic control, but rather whether it is at all possible to reach such results in real life. The Linköping Complication Study has shown very promising results in a population-based non-selected prospective cohort study.[2,3] Recently, others have published similar results.[4] Good metabolic control has been defined as a low HbA_{1c}, which is therefore an important goal.

HbA_{1c} measured with the same method in similar patient groups is known to differ remarkably between different clinics.[5] Despite such knowledge, which could affect treatment regimens, follow-up some years later has shown surprisingly stable differences.[6] Differences in populations might be one explanation, but even within very homogenous populations differences between clinics may still be pronounced,[7] demonstrating the crucial role of treatment.

HbA_{1c} levels are influenced by the glycemic control of the preceding 2-3 months.[8,9] Other factors, such as erythrocyte survival time and antioxidants, may affect the results,[10,11] but are probably of minor importance to the majority of patients. In healthy people with normal blood glucose (BG), young children have lower HbA_{1c} than adolescents and adults.[12] In adults, HbA_{1c} rises

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slowly with increasing age.[13]

Sometimes, however, the HbA_{1c} of a patient is surprising. A patient may have high HbA_{1c} in spite of relatively normal blood glucose values measured at home. In such cases our interpretation is usually that the BG tests do not reflect mean BG during recent days or weeks. There may be several explanations for this. Evidently, the home glucose results presented do not cover high BG values either for a certain time of the day (e.g., night time) or certain days of the week. Alternatively, there might have been a recent period with high BG values resulting in a heavy impact on the HbA_{1c} value. It has also been suggested that some patients may report false values, although this is rare in our experience. However, sometimes patients have a surprisingly low HbA_{1c} in spite of many correctly measured high BG values. This is more difficult to explain. As glycosylation of hemoglobin is initially reversible and needs a certain time to become irreversible,[14] one explanation may be that the high BG values represent very short peaks without influencing the stable fraction of HbA_{1c}. But other questions arise. How short do these peaks need to be not to influence HbA_{1c}? Is it less important for the HbA_{1c} of a patient if there are repeated high BG peaks than if there is a slightly increased stable BG concentration for the day? Perhaps certain individuals do not glycosylate hemoglobin as easily as others and therefore get lower HbA_{1c} in spite of high BG. In fact, patients with diabetes may differ in their ability to handle glucose overload, resulting in different HbA_{1c} despite the BG balance being the same.[15] Or does very low BG at a certain time of the day, e.g., during the night, compensate for high peaks during the rest of the day? As a glucose sensor gives an objective picture based on glucose determinations several times per minute over 24 hours, we have used such s.c. glucose profiles to answer the questions above. The aim of this study was to evaluate the relationship between the area under curve (AUC), measured by a continuous glucose monitoring system (CGMS), and HbA_{1c}.

Methods

Study design

A first-generation CGMS (Medtronic, Northridge, CA, USA) was used in this study.[16] The CGMS sensor monitors interstitial glucose levels (2.2–22 mmol/L) in subcutaneous tissue every 10 seconds and records an average value every 5 minutes.[17] The subcutaneous glucose oxidase electrode is viable for up to 72 hours. Data are downloaded to a computer that provides a continuous tracing of BG values in the form of daily BG profiles and a summary table of average glucose levels, glucose ranges, and standard deviations. The lag time between the CGMS and BG after a meal has been found to be 4 minutes in rise and 9 minutes in fall.[18]

The present paper is a post hoc analysis of the data from a previously published study,[19] in which type 1 diabetic patients with an HbA_{1c} of 6.8% or above (-7.9% DCCT level) were consecutively asked to participate until we had acquired 32 patients who agreed to participate. Informed consent was obtained from the patients and their parents. Half of the patients were randomized into an open study arm and the remaining patients into a blinded arm. Both arms had 8 pump users and 8 patients with multiple daily injections (MDI). Both study arms wore the CGMS for 3 days every 2 weeks and were instructed to complete at least two self-monitoring of BG (SMBG) measures at different times during the day and a 7-point SMGB once every week. Local anesthetic EMLA Cream (Astra, Södertälje, Sweden) was used before all insertions. Most of them used a special instrument (Senserter) to minimize insertion pain. During the blinded study arm period neither the patient nor members of the diabetes team reviewed the results. After 3 months, the open and blinded study arms crossed over for another 3 months. HbA_{1c} was determined before and after each 3-month study period. HbA_{1c} was determined by DCA 2000 (Bayer, Gothenburg, Sweden) and adjusted to the Swedish national standard,[20] which is supposed to be approximately 1.1% below the DCCT standard.[21] The determinations were also transformed mathematically, after which we computed a low BG index (LBGI) each day for each patient according to the method by Kovatchev et al.[22] A high LBGI indicates several low BG values, a few extreme low values or a combination of both. Glucose fluctuations were estimated by standard deviations (SD) of glucose readings.

One patient was excluded because of pregnancy, 1 had difficulty in managing the CGMS, and 3 found the protocol too demanding. The remaining 27 patients were aged 12.5±3.3 (mean and SD) years (range 5-19), with a type 1 diabetes duration of 7.0±3.9 (2-15) years.

All patients were treated with multiple insulin therapy (usually rapid-acting insulin analogs before meals plus twice daily intermediate-acting insulin, n=14) or insulin infusion pumps (n=13). Their baseline HbA_{1c} was 8.0±1.1% (range 6.8-10.8%). There were no significant differences between the two groups in respect of gender, duration of diabetes or other background factors (Table). Five patients did not complete the 12 sensor evaluation periods. However, their HbA_{1c} results were included in the statistical analysis on an intention-to-treat basis. In total, 130 of a possible 135 HbA_{1c} values were measured and included

in the analysis. In the calculations we included only 24-hour whole glucose areas, and excluded 24-hour profiles with short or long breaks. Owing to a number of malfunctions and other problems with monitoring (first generation), we were able to include only 449 profiles of a possible 1053 (43%).

Statistical analysis

The whole area under the s.c. glucose concentrationtime curve was calculated for each 24-hour period within the range of the CGMS (2.2–22 mmol/L or 40–400 mg/dl), using GraphPad Prism version 4.0a (GraphPad Software, San Diego, California, USA) as well as partial AUCs with cutoffs established at 10, 15 or 20 mmol/L. For instance, because each hour will have 12 values, an AUC 24-hour mmol/L of 3440 gives a mean value of 11.9 mmol/L for a particular day (3449/288, where 288 = 12 values multiplied with 24 hours). The number of peaks (>15.0 mmol/L) during the 24-hour period was also calculated and related to HbA_{1c}. HbA_{1c} was compared with the CGMS curves during the previous 3-month period and with shorter periods (1 month and 2 months) prior to the HbA_{1c} measurement. Linear regression analysis was used to evaluate the relationship between AUC and the HbA_{1c} levels. Mean values (mean ± SD) were compared using the Mann-Whitney *U* test.

Results

As analysis during the blinded and open study arm period showed no difference in relationship between s.c. glucose AUC and HbA_{1c}, the following analysis include all patients (both study arms were included).

When all 24-hour CGMS profiles during the 6-month study period were taken together, there was no relationship between HbA_{1c} values and s.c. glucose AUC (r=0.04) or between HbA_{1c} values and the number of peaks >15.0 mmol/L (r=0.04). This lack of relationship was also seen when comparing the HbA_{1c} values with three different baselines of AUC (10, 15 and 20 mmol/L). When the low HbA_{1c} values (<7%, 18 of 130 values) were excluded, a positive relationship was found between HbA_{1c} and the AUC above 20 mmol/L (r=0.17, P<0.03).

Children on pump treatment (13 patients, 216 profiles, mean BG 10.2 mmol/L ± 4.04 (SD)) showed no association between AUC and HbA_{1c}, whereas children with MDI (14 patients, 233 profiles, mean BG 11.1 mmol/L ± 4.32 (SD)) showed a significant relationship between the whole AUC (r=0.18, P<0.01), AUC >15 mmol/L (r=0.21, P<0.01) as well as the number of peaks >15.0 mmol/L (r=0.18, P<0.01), and HbA_{1c} during the study period. The SD difference between the two groups almost reached a significant level (P=0.07). The children with insulin infusion pumps tended to have higher mean HbA_{1c}, although not significantly higher than children with MDI (7.8±1.2 vs 7.5±0.7).

Individually, 12 patients (6 with pump and 6 with MDI, mean BG 10.4±4.13 mmol/L) showed a positive relationship between HbA_{1c} and AUC, exemplified by Fig. 1A. They had generally high BG values but less fluctuation (Fig. 2). When using 15 mmol/L as baseline, and only calculating the area above that value, the association between HbA_{1c} and AUC was negative (Fig. 1B). Five patients (2 with pump, mean BG 10.7 ±4.31 mmol/L) had the opposite pattern: a negative

Table. Some background data of the two groups of patients

Treatment	Mean age (y)	Boys	Girls	Duration of diabetes (y)	HbA_{1c} at start	HbA_{1c} after 24 wk	Insulin at start (U/kg)
MDI	11.6	5	8	5.8	7.8	7.4	1.1
Pump	13.3	5	9	8.3	8.2	7.7	1.0
P value	0.18			0.10	0.26	0.61	0.54

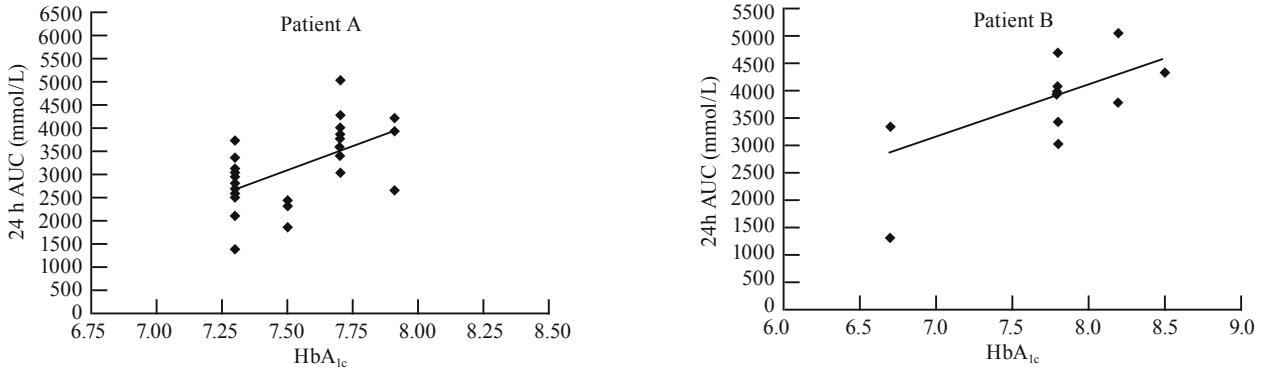

Fig. 1A. Certain patients displayed a clearly positive relationship between HbA_{1c} and the whole AUC, as exemplified by patients A and B.

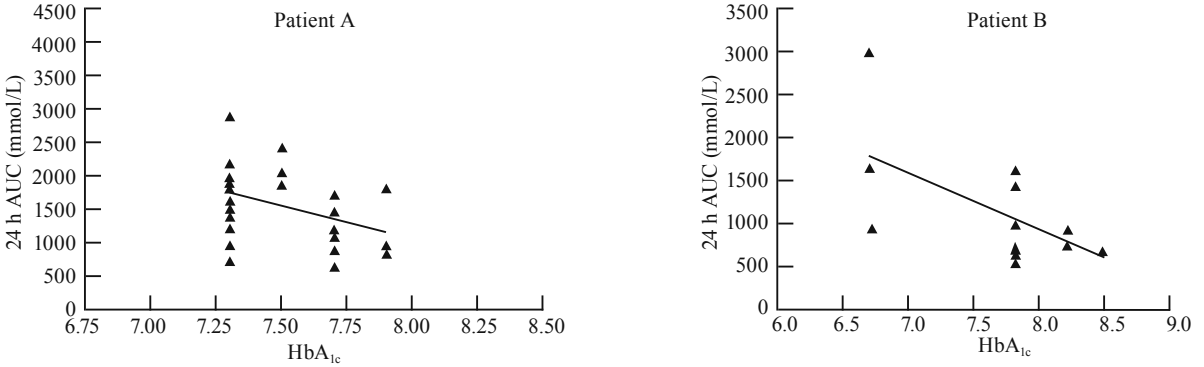

Fig. 1B. Certain patients displayed a negative relationship between HbA_{1c} and AUC at baseline 15 mmol/L, as exemplified by patients A and B.

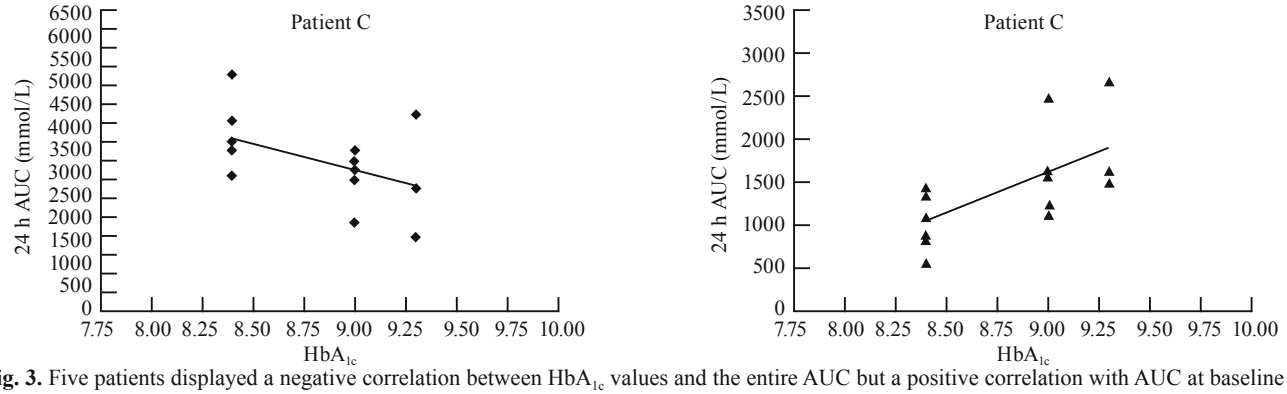

Fig. 3. Five patients displayed a negative correlation between HbA_{1c} values and the entire AUC but a positive correlation with AUC at baseline 15 mmol/L, as exemplified by patient C.

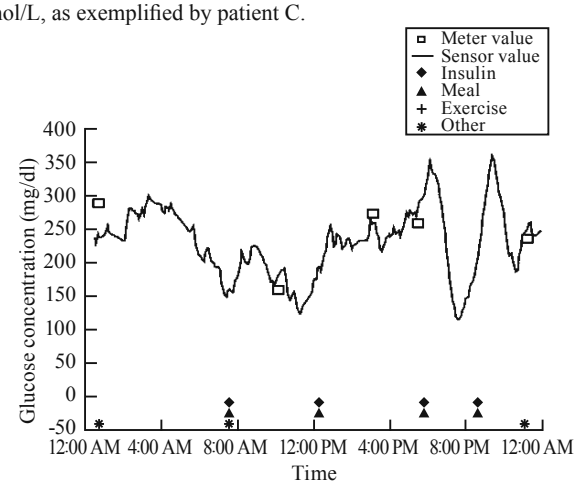

Fig. 2. Individuals with a positive correlation between the entire AUC and HbA_{1c} generally displayed fewer fluctuations in blood glucose values, as exemplified by this patient (boy, 15 years, HbA_{1c} 6.9% at the beginning of the study).

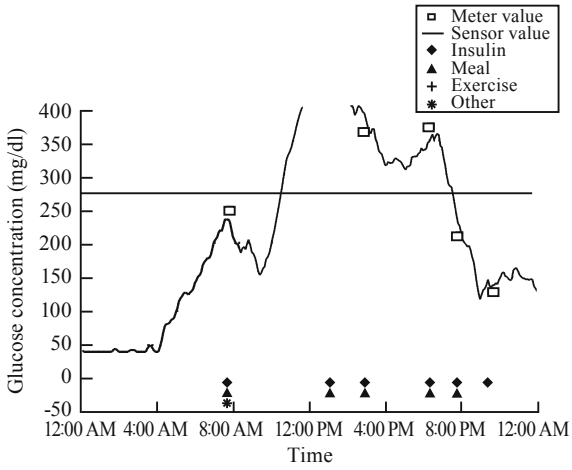

Fig. 4. Five patients displayed a negative correlation between HbA_{1c} values and the entire AUC but a positive correlation with AUC at baseline 15 mmol/L, indicated by the line, as exemplified by this patient (girl, 12 years, HbA_{1c} 7.3% at the beginning of the study). These patients had wide fluctuations in blood glucose.

correlation between HbA_{1c} values and the whole AUC but a positive correlation with AUC above baseline 15 mmol/L (Fig. 3). These patients had wide fluctuations in BG (Fig. 4) and significantly higher mean HbA_{1c} values (8.0% vs 7.4%, $P<0.01$). When a one-way ANOVA was performed with SD, AUC and mean BG as covariates, pump use was not significant and explained only a minor part of the difference in HbA_{1c}.

HbA_{1c} levels 12 weeks after wearing the CGMS device were significantly lower than baseline values, 7.7 and 7.3, respectively ($P<0.03$). The open study arm was the most responsible for this pattern, 7.7 and 7.2, respectively ($P<0.03$), whereas the difference in the blind arm did not reach a significant level, 7.7 and 7.5 respectively.

There was no correlation between mean sensor

glucose value and the HbA_{1c} values during the study period (r=0.03) nor between HbA_{1c} values and upper (r=0.03) or lower range (r=0.06) sensor glucose values. Nor did we find any correlation between the SD of BG and HbA_{1c} in the whole group (r=0.001), in the children with the pump (r=0.04), or in the other children (r=0.04).

As with the CGMS profiles during the 6-month period, there was no overall relationship between HbA_{1c} and LBGI (r=0.000001) if only HbA_{1c} values <7 were included or if only HbA_{1c} values >7 were included.

There was a clearly negative correlation between LBGI and the s.c. glucose AUC (r=0.61, P<0.001) and an even stronger, but now positive, correlation when AUC above 15 mmol/L was calculated (r=0.75, P<0.0001). The correlation was also positive above baseline 10 mmol/L (r=0.38, P<0.01).

On division into treatment groups, there was no relationship regarding the children on pump treatment, whereas the children on MDI displayed a negative relationship between LBGI and HbA_{1c} (r=0.29, P< 0.001).

Discussion

Significant relationships have been found between BG profiles and glycosylated hemoglobin.[23] In the Diabetes Control and Complications Trial (DCCT) study, there was a strong significant correlation between the mean blood glucose values (MBG) of 7-point glucose profiles and HbA_{1c}, although there was a very wide range of individual relationships.[24] However, large numbers of patients had consistently non-random, large positive or negative deviations from the predicted HbA_{1c} in their observed HbA_{1c}, based on the associated MBG.[25] Night time values were available in <1% of the profiles. Although we recorded CGMS for 3 days every 2 weeks, the daily "snapshots" of the glucose profiles in our study hardly represented the average glucose profiles during the observation period. However, in spite of recording only a few days of s.c. glucose levels, several studies have shown a significant correlation between BG, AUC and HbA_{1c} when CGMS was used. Thus, Deiss et al[26] found that HbA_{1c} was correlated both with the CGMS AUC and MBG in 50 children. Alemzedah et al[27] found a significant correlation between MBG and HbA_{1c} (r^2=0.22, P<0.009) in 30 pediatric patients when using 48 hours of CGMS data, and Fiallo-Scharer[28] found a correlation of 0.40 (P<0.001) between MBG and HbA_{1c} during 70-hour use of CGMS. This may be surprising, as we know from everyday experience at the diabetes clinic that, when downloading BG meters, MBG often varies from week to week depending on activity, recurrent illness, etc although HbA_{1c} is relatively stable.

In contrast, in the current study we did not find a significant relationship between MBG or AUC and HbA_{1c} in spite of registration with CGMS repeatedly 3 days every second week over 2 months. In addition, the original study found a difference in HbA_{1c} between the two arms, but we could not find a difference in the relationship between AUC and HbA_{1c} when the two arms were analyzed separately.

The most probable explanation for our lack of relationship may be technical, i.e., that we used the first generation of CGMS sensors. Another explanation could be that the patients were influenced by wearing sensors and therefore to some extent changed their life. Often patients do not live their normal life when they know that their BG is constantly registered. This might have contributed to the lack of correlation between AUC and HbA_{1c}, especially as this was their first experience using CGMS. Patients with higher BG levels and HbA_{1c} might try harder to have lower BG values during the days they wore the CGMS monitor. Moreover, as patients often used the sensors on the same weekdays, scheduled activities may have contributed to a non-representative glucose profile during the CGMS days. We did find some significant correlations between AUC and HbA_{1c} in the MDI group, but not in the group with CSII, which might mean that the CSII group found it easier to adjust their way of living and/or correct high and low BG readings during the days they wore the sensor. CGMS did not show a significantly different SD of glucose measurements when compared with eight occasions of daily BG self-monitoring (3.9 vs 4.5 mmol/L, P>0.05).[29] A slightly lower SD of the BG profiles was found in the DCCT study when pump and MDI therapy were compared (2.75 mmol/L vs 3.11 mmol/L, P=0.09).[30] In addition, the large biological variation of glycation that affects HbA_{1c}[31] may have influenced the results in our study although all of the participants were of Caucasian origin. In one study, 29% of the patients had HbA_{1c} levels that were significantly higher or lower than predicted by the regression equation between HbA_{1c} and MBG.[32] In an experimental model, a fluctuating BG level has been shown to be more harmful than a constantly elevated BG level, presumably because there is less opportunity of developing protecting mechanisms.[33]

Patients in the DCCT study with the same average HbA_{1c} throughout the 9 years the study progressed, but different types of insulin treatment, were compared.[34] Somewhat surprisingly, there was a clear difference, i.e., a considerably increased risk of visual impairment, when they were on conventional treatment than when they were given intensive treatment. With 1-2 doses per day, the average HbA_{1c} must be reduced to 7% to avoid

progression of retinopathy, whereas in the intensive treatment group HbA_{1c} was above 8% before this was observed. The interesting question here is whether this reflects a shortcoming in HbA_{1c} in reflecting the risk of vascular complications in that MBG would have better reflected the risk of complications. Or is there another factor that influences the risk, for example the fluctuation in BG as such and perhaps only above a certain BG level? Evidence suggests that the fluctuation of BG measured as SD has a low influence on the HbA_{1c} level (7% of that of MBG)[35] or none at all.[36] However, these studies are limited by analyzing only a very small number of BG measurements during the day and none during the night. According to the DCCT study, the variability (SD) of within-day BG did not contribute to either retinopathy or nephropathy.[30]

To our knowledge, no other study has repeatedly registered CGMS over such a long time as we did. It is therefore noteworthy that we found subsets of patients with significant correlations between AUC and CGMS. Patients with a positive correlation between AUC above baseline 15 mmol/L and HbA_{1c} generally had less fluctuation of BG and higher HbA_{1c}. On the other hand, patients with a negative correlation between AUC above 15 mmol/L and HbA_{1c} had wide fluctuations and lower HbA_{1c} than did the previous group. The present study indicates that the glucose fluctuations above 15 mmol/L per se contribute to a higher HbA_{1c} level and could explain why the relationship between AUC or MBG was not significant. The possible negative effect of wide BG fluctuations, which may occur above a certain BG threshold, is clinically important knowledge and may be one of the explanations for the above-mentioned findings in the DCCT study. The pump group had lower fluctuations in their glucose readings than did the MDI group, which is in accordance with the findings of Pickup et al[37] in adults. These findings remain to be further explored in a study of a larger number of patients.

In conclusion, in the present study we did not find any overall significant relationship between AUC or MBG and HbA_{1c}. However, in MDI patients who had wider BG fluctuations, there was a significant relationship between AUC and HbA_{1c}. This indicates that BG fluctuations as such, especially at high BG levels, may influence HbA_{1c} and the risk of complications. Therefore, this may also indicate that therapeutic interventions should aim at reducing BG fluctuations.

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