Does Glucose Variability Influence the Relationship Between Mean Plasma Glucose and HbA_{1c} Levels in Type 1 and Type 2 Diabetic Patients?

The Harvard community has made this article openly available.
Please share how this access benefits you. Your story matters.

Citation
Kuenen, Judith C., Rikke Borg, Dirk J. Kuik, Hui Zheng, David Schoenfeld, Michaela Diamant, David M. Nathan, and Robert J. Heine. 2011. Does glucose variability influence the relationship between mean plasma glucose and HbA_{1c} levels in type 1 and type 2 diabetic patients?. Diabetes Care 34(8): 1843-1847.

Published Version
doi:10.2337/dc10-2217

Accessed
July 5, 2017 9:51:43 AM EDT

Citable Link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:10464973

Terms of Use
This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)
Does Glucose Variability Influence the Relationship Between Mean Plasma Glucose and HbA1c Levels in Type 1 and Type 2 Diabetic Patients?

Judith C. Kuennen, MD
Rikke Borg, MD
Dirk J. Kuk, MSC
Hui Zheng, PhD
David Schoenfeld, PhD

Michaela Diamant, MD
David M. Nathan, MD
Robert J. Heine, MD

On behalf of the ADAG Study Group*

OBJECTIVE—The A1C-Derived Average Glucose (ADAG) study demonstrated a linear relationship between HbA1c and mean plasma glucose (MPG). As glucose variability (GV) may contribute to glycation, we examined the association of several glucose variability indices and the MPG-HbA1c relationship.

RESEARCH DESIGN AND METHODS—Analyses included 268 patients with type 1 diabetes and 139 with type 2 diabetes. MPG during 3 months was calculated from 7-point self-monitored plasma glucose and continuous glucose monitoring. We calculated three different measures of GV and used a multiple-step regression model to determine the contribution of the respective GV measures to the MPG-HbA1c relationship.

RESULTS—GV, as reflected by SD and continuous overlapping net glycemic action, had a significant effect on the MPG-HbA1c relationship in type 1 diabetic patients so that high GV led to a higher HbA1c level for the same MPG. In type 1 diabetes, the impact of confounding and effect modification of a low versus high SD at an MPG level of 160 mg/dL on the HbA1c level is 7.02 vs. 7.43 and 6.96 vs. 7.41. All GV measures showed the same tendency.

CONCLUSIONS—In only type 1 diabetic patients, GV shows a significant interaction with MPG in the association with HbA1c. This effect is more pronounced at higher HbA1c levels. However, the impact of GV on the HbA1c level in type 1 diabetes is modest, particularly when HbA1c is close to the treatment target of 7%.

During the lifetime of the erythrocyte, hemoglobin (Hb) is gradually glycated. The proportion of the glycated sites, HbA1c, within the erythrocyte increases throughout its life span and reflect the exposure to mean blood glucose (MBG) levels during the preceding 2–3 months (3). This non-enzymatic posttranslational modification is relatively slow. In vivo and in vitro studies have shown that HbA1c levels are directly proportional to the time-averaged concentration of glucose during the erythrocyte’s life span (3–6). Given the kinetics of glycation, brief periods of hyperglycemia should not have a major impact on HbA1c levels (7–9).

However, increased glycated protein levels are documented in some nondiabetic pathological states. So, hyperglycemia is not the complete answer to the etiology of increased early glycated products in nondiabetic conditions. A common denominator is oxidative stress. It has been hypothesized that oxidative stress either via increasing reactive oxygen species or by depleting the antioxidants may modulate the genesis of early glycated proteins in vivo (10,11). Hyperglycemia stimulates oxidative stress (12) and glucose variability; in particular, postprandial glucose excursions have been regarded as potentially deleterious as a result of, among other factors, their association with the increase of oxidative stress (13). Therefore, glucose variability (GV) could influence the glycation of HbA1c.

Previous studies have examined whether the relationship between mean plasma glucose (MPG) levels and HbA1c is influenced by glucose variability and found no or minimal influence (10,14,15). However, these studies used limited self-monitoring of blood glucose (SMBG) data to assess mean glucose levels and variability in relatively small numbers of measurements. These methods could underestimate glycemic excursions. Continuous glucose monitoring (CGM) provides a more complete view of glycemic excursions, including the duration and frequency of the excursions, and allows calculation of features of GV. Our aim was to examine the influence of GV on the MPG-HbA1c relationship in the A1C-Derived Average Glucose (ADAG) study.

RESEARCH DESIGN AND METHODS—The ADAG study was conducted at 10 centers in the U.S.,...
Glucose variability, plasma glucose, and HbA$_{1c}$

Europe, and Africa from 2006 to 2008 to define the relationship between HbA$_{1c}$ and average glucose levels. Because a full description of this observational study has been published (14), we describe it here only briefly. A total of 268 individuals with type 1 diabetes and 159 individuals with type 2 diabetes (age 18–70 years) completed the study. Participants were selected based on stable glycemic control as evidenced by two HbA$_{1c}$ values within one percentage point of each other in the 6 months prior to recruitment. Individuals with a wide range of HbA$_{1c}$ levels were included.

Participants with conditions leading to major changes in glycemia (infectious disease, steroid therapy, and pregnancy) or conditions that might interfere with the measurement of HbA$_{1c}$ or the relationship between HbA$_{1c}$ and MPG (hemoglobinopathies [16], anemia, increased erythrocyte turnover, blood loss and/or transfusions, or chronic renal or liver disease) were excluded (14). The study was approved by the human studies committees at the participating institutions, and informed consent was obtained from all participants.

Measurements of glycemia

During the study period, CGM (Medtronic Minimed, Northridge, CA) was performed at home four times with 4-week intervals during the 16-week study period. Monitoring period lasted at least 48 h, during which time glucose levels were assessed every 5 min. CGM data were accepted for analysis if there were no gaps longer than 120 min and if the mean absolute difference with the Hemocue calibration results was <18%, as recommended by the manufacturer. For calibration purposes, participants performed SMBG with the Hemocue meter (Hemocue, Angelholm, Sweden) during the days of CGM.

For adequate calculation of MPG, subjects additionally performed a seven-point SMBG (OneTouch Ultra; Lifescan, Milipitas, CA) for at least 3 days per week during the weeks when CGM was not performed. All blood glucose values stated are plasma equivalents.

HbA$_{1c}$ samples were analyzed with four highly intercorrelated DCCT-aligned assays: a high-performance liquid chromatography assay, two immunoassays, and an affinity assay (all approved by the National Glycohemoglobin Study Program). The mean HbA$_{1c}$ value at the end of the 12 week study period was used (14).

Calculating glucose variability

Three indices of intraday glucose variability were calculated based on CGM: the SD of mean glucose concentrations, the mean amplitude of glycemic excursions (MAGE), and the continuous overlapping net glycemic action (CONGA). High SD, MAGE, and CONGA values indicate high intraday glucose variability. MAGE is the mean of the differences between consecutive peaks and nadirs, only including changes of >1 SD of glycemic values and thus capturing only major fluctuations (17). For the calculation of CONGA, the difference of the current value compared with the value n hours previously was calculated for each observation after the first n hours. The CONGA is the SD of these differences (18). In the analyses, we used CONGA at 4 h (CONGA4). Calculations based on CGM data were calculated after exclusion of the initial 2 h of monitoring, which is considered to be an unstable calibration period.

Statistical analysis

First, we explored the correlations between MPG and HbA$_{1c}$, and measures of glycemic variability as SD, MAGE, and/or CONGA for the total diabetic population and the two diabetes types. Multiple linear regression was used to investigate confounding and effect-modifying influence of clinical parameters (glycemic variability) on the relation between the determinant (MPG) and outcome (HbA$_{1c}$) of interest. We then assessed which of the variability measures (SD, MAGE, or CONGA) had the strongest impact on the MPG-HbA$_{1c}$ relationship by confounding or effect modification.

Effect modification was concluded when the slope of the interaction term of glycemic variability and determinant was significant. If no effect modification might be concluded, a parameter $\Delta B$ was computed as the relative difference of the slope of the determinant in the model without and with the clinical parameter. Confounding was concluded when the absolute value of $\Delta B$ exceeded the generally accepted threshold of 10%.

Multivariate confounding was investigated with a variant of stepwise regression, in which the stepping criterion was not a $P$ value but the $\Delta B$ as long as it exceeded the threshold. For significance, a threshold of $\alpha = 0.05$ was used.

Analyses were done for the total population and stratified for the type of diabetes. Finally, we illustrated the magnitude of the effect caused by the variability indices, by confounding or effect modification, on the MPG-HbA$_{1c}$ relationship.

RESULTS—Of the 507 patients enrolled, 427 completed the study and had adequate glucose monitoring and HbA$_{1c}$ samples for inclusion in the analyses. Two hundred and sixty-eight participants had type 1 diabetes, and 159 had type 2 diabetes. The CGM and the SMBG data during the 3-month period included approximately 2,400 and 300 measurements per subject, respectively. The relationship between the HbA$_{1c}$ level at the end of the 3-month study period and MPG calculated over the preceding 3 months was expressed as the simple linear regressions.

The formula for the total diabetic population was as follows: HbA$_{1c}$ (%) = 0.028 × MPG (mg/dL) + 2.66 ($R^2 = 0.80$). The formula for type 1 diabetes was as follows: HbA$_{1c}$ (%) = 0.028 × MPG (mg/dL) + 2.77 ($R^2 = 0.77$). The formula for type 2 diabetes was as follows: HbA$_{1c}$ (%) = 0.028 × MPG (mg/dL) + 2.62 ($R^2 = 0.82$).

The clinical and glycemic characteristics are shown in Table 1. Mean HbA$_{1c}$ (SD) for type 1 diabetic patients was 7.3% (1.1) and for type 2 diabetic patients was 6.8% (1.1).

All GV measures had significant influence on the MPG-HbA$_{1c}$ relationship for the total population. The variability index SD showed the strongest influence on the MPG-HbA$_{1c}$ relationship. None of the GV measures showed confounding for all diabetic patients pooled or for the type 1 or type 2 diabetic patients separately (Table 2).

In the type 1 diabetic patients, the effect modification of SD and CONGA showed the strongest influence on the MPG-HbA$_{1c}$ relationship. None of these measures showed confounding for all diabetic patients pooled or for the type 1 or type 2 diabetic patients separately.

The MPG-HbA$_{1c}$ linear regression formula with effect modification for type 1 diabetes was as follows: HbA$_{1c}$ (%) = 2.64 + 2.63 × MPG/100 + 0.58 × SD/100. The MPG-HbA$_{1c}$ linear regression formula with effect modification for type 2 diabetes was as follows: HbA$_{1c}$ (%) = 3.91 + 1.79 × MPG/100 - 1.37 × SD/100 + 1.25 × MPG/100 × SD/100. The impact of effect modification of low GV (SD = 30 mg/dL) versus high GV (SD = 100 mg/dL) for an MPG level of 160 mg/dL in type 1 diabetes on the HbA$_{1c}$ level was 6.96 vs. 7.41%, respectively, as shown in Table 3. At an MPG level of 220 mg/dL (HbA$_{1c}$ following the regression formula of 8.89%), a decline in the SD parameter from 100 to 30 mg/dL reduced HbA$_{1c}$ from 9.23 to 8.26%.
CONCLUSIONS

For all patients pooled, there was no effect modification of the respective GV measures on the MPG-HbA1c relationship. For type 2 diabetic patients, the impact of effect modification from the respective GV measures was far from significant (Table 2). The number of patients with a predefined SD is shown in Table 1 for all patients pooled and for the type 1 and type 2 diabetic patients separately.

CONCLUSIONS—This study demonstrated a significant effect of GV, as reflected by SD, on the MPG-HbA1c relationship. High GV (SD) is associated with higher HbA1c levels for a given MPG, and this effect was more pronounced at higher HbA1c and MPG values. However, the magnitude of this effect of GV was small and only demonstrable in type 1 diabetic patients. Possibly, the type 2 diabetic patient group was too small (n = 159) and the variability in this group too low to find this interaction.

The ADAG study showed a tight correlation between HbA1c and MPG, allowing the translation of HbA1c into estimated average glucose (14,19). It has been suggested that GV could affect the MPG-HbA1c relationship, but this has not previously been demonstrated (20–22). To our knowledge, the current study is the largest study reporting an influence of GV—as expressed by SD, MAGE, and CONGA4 calculated from CGM—on the MPG-HbA1c relationship. The discrepancies in the MPG-HbA1c relationship are less likely caused by technical errors because this study included accurate and centralized measurements of HbA1c values and intensively measured plasma glucose concentrations (~2,700 values) in a large and diverse population. Also, individuals with conditions or treatment that might result in major changes in glycemia or interference with the HbA1c assay, or the MPG-HbA1c relationship, were excluded. These precautions allowed us to search for factors other than MPG that may contribute to HbA1c.

In general, GV is higher in patients with poor glycemic control and in type 1 diabetic patients compared with type 2 diabetic patients, which can be attributed to insulin therapy and higher insulin sensitivity. High GV may affect glycation because of periodic exposure of the erythrocyte to high glucose levels and therefore to faster irreversible glycation.

Other factors like hyperglycemia-induced oxidative stress may affect the glycation process. In recent literature, it has been speculated that oxygen free radicals per se or with an associated decrease in antioxidants may modulate the formation of early glycated protein (10,11).

Brownlee (12) demonstrated that hyperglycemia stimulates oxidative stress. High GV and especially postprandial glucose excursions were also previously

### Table 1—Baseline clinical and glycemic characteristics

|                     | All         | Type 1 diabetes | Type 2 diabetes |
|---------------------|-------------|-----------------|-----------------|
| n                   | 427         | 268             | 159             |
| Age (years)         | 47.6 ± 13.6 | 44.1 ± 12.9     | 56.6 ± 9.4      |
| Sex (% female)      | 54          | 52              | 51              |
| Ethnicity (% non-Hispanic whites) | 83 | 93             | 73              |
| Current smokers     | 11          | 12              | 9               |
| Insulin treatment   | 76          | 100             | 38              |
| Glycemic measures   |             |                 |                 |
| HbA1c (%)           | 6.8 ± 1.3   | 7.3 ± 1.1       | 6.8 ± 1.1       |
| MPG (mg/dL)         | 149.4 ± 39.6| 162 ± 36        | 149.4 ± 36      |
| Measures of GV      |             |                 |                 |
| CGM SD (mg/dL)      | 48.6 ± 25.2 | 64.8 ± 16.2     | 39.6 ± 16.2     |
| MAGE (mg/dL)        | 86.4 ± 43.2 | 113.2 ± 32.4    | 68.4 ± 27       |
| CONGA4 (mg/dL)      | 66.6 ± 28.8 | 88.2 ± 23.4     | 52.2 ± 21.6     |
| SD (mg/dL)          |             |                 |                 |
| <30                 | 61 (14.3)   | 9 (3.4)         | 52 (32.7)       |
| 30–60               | 173 (40.5)  | 84 (31.3)       | 89 (36)         |
| <60–90              | 173 (40.5)  | 155 (57.8)      | 18 (11.3)       |
| >90                 | 20 (4.7)    | 20 (7.5)        | 0 (0)           |

Data are means ± SD, %, or n (%).

### Table 2—The P values of the influence of the respective GV measures themselves, as well as effect modification and the Δ of confounding, calculated from the respective slopes (B and B’) from the regression equations, on the HbA1c-MPG relationship for all patients pooled and for type 1 and type 2 diabetic patients separately

|                     | Influence of the GV measure (P) | Slope of MPG (B) in the main regression formula | Slope of MPG (B’) in the regression formula with the GV measure | ΔConfounding (%) | Effect modification (P) |
|---------------------|---------------------------------|-------------------------------------------------|---------------------------------------------------------------|----------------|------------------------|
| SD                  |                                 |                                                |                                                               |                |                        |
| All                 | <0.01                           | 2.818                                          | 2.624                                                         | 6.9            | 0.06                   |
| Type 1 diabetic     | 0.01                            | 2.781                                          | 2.631                                                         | 5.4            | <0.01                  |
| Type 2 diabetic     | 0.06                            | 2.782                                          | 2.637                                                         | 5.2            | 0.74                   |
| MAGE                |                                 |                                                |                                                               |                |                        |
| All                 | <0.01                           | 2.818                                          | 2.700                                                         | 4.2            | 0.37                   |
| Type 2 diabetic     | 0.19                            | 2.781                                          | 2.721                                                         | 2.2            | 0.06                   |
| Type 2 diabetic     | 0.19                            | 2.782                                          | 2.698                                                         | 3.0            | 0.19                   |
| CONGA4              |                                 |                                                |                                                               |                |                        |
| All                 | <0.01                           | 2.818                                          | 2.667                                                         | 5.4            | 0.15                   |
| Type 1 diabetic     | 0.06                            | 2.781                                          | 2.687                                                         | 3.4            | 0.02                   |
| Type 2 diabetic     | 0.07                            | 2.782                                          | 2.661                                                         | 4.3            | 0.46                   |

*ΔConfounding in % = 100 × absolute (B’ – B)/B.
Glucose variability, plasma glucose, and HbA1c

Table 3—Quantification or impact of confounding or effect modification for type 1 diabetic patients of a low vs. a high SD for a given MPG on the HbA1c level next to the HbA1c values calculated with the regression formula for type 1 diabetes

| MPG [mg/dL] (mmol/L) | Regression formula | Confounding | Effect modification |
|----------------------|-------------------|-------------|-------------------|
|                      | HbA1c (%)         | SD 30 mg/dL | SD 100 mg/dL      | SD 30 mg/dL | SD 100 mg/dL      |
| 140 (7.8)            | 6.67              | 6.50        | 6.90              | 6.53        | 6.80              |
| 160 (8.9)            | 7.22              | 7.02        | 7.43              | 6.96        | 7.41              |
| 180 (10)             | 7.78              | 7.55        | 7.95              | 7.39        | 8.02              |
| 200 (11.1)           | 8.34              | 8.08        | 8.48              | 7.83        | 8.62              |
| 220 (12.2)           | 8.89              | 8.60        | 9.01              | 8.26        | 9.23              |
| 240 (13.3)           | 9.45              | 9.13        | 9.53              | 8.69        | 9.84              |

Limitations of our study are that CGM has a limited range of reliable measurements between 2.2 mmol/L and 22.2 mmol/L. Therefore, theoretically, CGM performance could be less precise in patients with high glycemic variability. Furthermore, CGM has a lag time in glucose values compared with venous measured values (the physiological gap), and this can result in underestimation of the influence of GV on the glycation of HbA1c, and no measures of erythrocyte survival, oxidative stress, or clinical follow-up are available in this population.

In conclusion, at higher levels of GV the relationship between HbA1c and MPG in patients with type 1 diabetes is altered, leading to a higher HbA1c level for a given MPG. However, the impact (near the HbA1c treatment target of 7%) is only modest.

Acknowledgments—The ADAG study is supported by research grants from the American Diabetes Association and the European Association for the Study of Diabetes.

Financial support was provided by Abbott Diabetes Care, Bayer Healthcare, GlaxoSmithKline, sanofi-aventis Netherlands, Meck & Company, LifeScan, and Medtronic Minimed. Supplies and equipment were provided by Medtronic Minimed, LifeScan, and Hemocue. R.J.H. is employed by and owns stocks of Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

J.C.K. researched data, contributed to discussion, and wrote the manuscript. R.B. researched data, contributed to discussion, and edited the manuscript. D.J.K., H.Z., and D.S. researched data. M.D. contributed to discussion and edited the manuscript. D.M.N. reviewed and edited the manuscript. R.J.H. contributed to discussion and reviewed and edited the manuscript.

Parts of this study were presented in abstract form at the 44th Annual Meeting of the European Association for the Study of Diabetes (Poster number 1065), 7–11 September 2008, Rome, Italy and at the 68th Scientific Sessions of the American Diabetes Association, San Francisco, California, 6–10 June 2008.

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;329:977–986.

2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853.

3. Bunn HF, Haney DN, Kamin S, Gabby KH, Gallop PM. The biosynthesis of human hemoglobin A1c. Slow glycosylation of hemoglobin in vivo. J Clin Invest 1976;57:1652–1659.

4. Beach KW. A theoretical model to predict the behavior of glycosylated hemoglobin levels. J Theor Biol 1979;81:547–561.

5. Fluckiger R, Winterhalter KH. In vitro synthesis of hemoglobin A1c. FEMS Lett 1976;7:356–360.

6. Huggins P, Bunn HF. Kinetic analysis of the nonenzymatic glycosylation of hemoglobin. J Biol Chem 1981;256:5204–5208.

7. Bunn HF, Gabby KH, Gallop PM. The glycosylation of hemoglobin: relevance to diabetes mellitus. Science 1978;200:21–27.

8. Gonen B, Rubenstein A, Rochman H, Tanega SP, Horwitz DL. Haemoglobin A1c: an indicator of the metabolic control of diabetic patients. Lancet 1977;2:734–737.

9. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin A1c in diabetes mellitus. N Engl J Med 1976;295:417–420.

10. Selvaraj N, Bobby Z, Sathiyapriya V. Effect of lipid peroxides and antioxidants on glycation of hemoglobin: an in vitro study on human erythrocytes. Clin Chim Acta 2006;366:190–195.

11. Selvaraj N, Bobby Z, Sridhar MG. Oxidative stress: does it play a role in the genesis of early glycated proteins? Med Hypotheses 2008;70:265–268.

12. Brownlee M. A radical explanation for glucose-induced beta cell dysfunction. J Clin Invest 2003;112:1788–1790.

13. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681–1687.

14. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Alc-Derived Average Glucose Study Group. Translating associated with oxidative stress in type 2 diabetes (13). The activation of oxidative stress, estimated from urinary excretion rates of isoprostanes, was highly correlated with MAGE calculated from CGM (13). However, Wentholt et al. (23) could not replicate these results in type 1 diabetes. Recently, Ceriello et al. (15) demonstrated that high intraday GV was more damaging to endothelial function than stable hyperglycemia and that oxidative stress plays a key role. Whether oxidative stress influences glycation needs to be determined.

On the other hand, it has been demonstrated that erythrocyte survival is shorter at chronic high glucose concentrations levels, which might falsely lower HbA1c levels. Peterson et al. (24) showed that the life span of 51Cr-labeled erythrocytes increased in all seven subjects when their poorly controlled diabetes was adequately treated. Virtue et al. (25) concluded that there is a hyperglycemia-related decrease in erythrocyte survival as measured by carbon monoxide in the expired air, which results in an exponential underestimation of the severity of hyperglycemia at higher HbA1c levels. Similarly, hyperglycemia-related osmotic stress may influence erythrocyte permeability and could cause damage to the erythrocyte and shorten its life span. These findings could lead to underestimation of HbA1c at higher MPG levels, concealing a glycemic control worse than indicated by HbA1c measurements. However, we found that type 1 diabetic patients with high GV display higher HbA1c levels than suspected based on MPG. This effect was more pronounced at higher HbA1c levels, indicating that focus on reducing GV, especially in patients with poor glycemic control, could help reduce HbA1c levels.
the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478
15. Ceriello A, Esposito K, Picconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 2008;57:1349–1354
16. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. Clin Chem 2001;47:153–163
17. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes 1970;19:644–655
18. McDonnell CM, Donath SM, Vidmar SI, Werther GA, Cameron FJ. A novel approach to continuous glucose analysis utilizing glycemic variation. Diabetes Technol Ther 2005;7:253–263
19. Consensus Committee. Consensus statement on the Worldwide Standardization of the Hemoglobin A1C Measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care 2007;30:2399–2400
20. Derr R, Garrett E, Stacy GA, Saudek CD. Is HbA1c affected by glycemic instability? Diabetes Care 2003;26:2728–2733
21. Service FJ, O’Brien PC. Influence of glycemic variables on hemoglobin A1c. Endocr Pract 2007;13:350–354
22. McCarter RJ, Hempe JM, Chalwe SA. Mean blood glucose and biological variation have greater influence on HbA1c levels than glucose instability: an analysis of data from the Diabetes Control and Complications Trial. Diabetes Care 2006;29:352–355
23. Wentholt IM, Kulik W, Michels RP, Hoekstra JB, DeVries JH. Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. Diabetologia 2008;51:183–190
24. Peterson CM, Jones RL, Koenig RJ, Melvin ET, Lehrman ML. Reversible hematologic sequelae of diabetes mellitus. Ann Intern Med 1977;86:425–429
25. Virtue MA, Fumie JK, Nuttall FQ, Levitt MD. Relationship between GHB concentration and erythrocyte survival determined from breath carbon monoxide concentration. Diabetes Care 2004;27:931–935