# Respective contributions of glycemic variability and mean daily glucose as predictors of hypoglycemia in type 1 diabetes: are they equivalent or not?

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## Abstract

### Objective

Evaluation of the respective contributions of short-term glycemic variability and mean daily glucose concentration to the risk of hypoglycemia in type 1 diabetes.

### Research design and methods

One hundred persons with type 1 diabetes investigated at the University Hospital of Montpellier (France) underwent continuous glucose monitoring (CGM) on two consecutive days (total of 200 24-h glycemic profiles). The following parameters were computed: the mean daily glucose exposure, (MDG), within-day glycemic variability (coefficient of variation for glucose, %CV), and the risk for hypoglycemia represented as percentage of time spent below three glycemic thresholds of 3.9, 3.45 and 3.0 mmol/L.

### Results

MDG and %CV were significantly ($p < 0.001$) higher or lower, respectively, when comparing the 24-h glycemic profiles according to whether no time or certain duration of time was spent below the thresholds. Univariate regression analyses showed that the MDG and %CV were the two explanatory variables that entered the model with the outcome variable (the time spent below the thresholds). The Classification And Regression Tree (CART) procedure indicated that the predominant predictor for hypoglycemia was %CV when the threshold was 3.0 mmol/L. In people with a mean glucose value ≤ 7.8 mmol/L, the time spent below 3.0 mmol/L was lowest ($p < 0.001$) when the %CV was below 34%.

### Conclusions

In type 1 diabetes, short-term glycemic variability relative to the mean glucose, i.e. %CV, explains more hypoglycemia than mean glucose alone when glucose threshold is 3.0 mmol/L. Minimizing the risk of hypoglycemia requires a %CV below 34%.

Key words: Mean glucose, glucose variability, hypoglycemia, type 1 diabetes

## Introduction

It is well known that the fear of hypoglycemia is a major barrier in the optimization of insulin therapy in persons with type 1 diabetes (T1DM) [1,2] who prefer less stringent glycemic targets rather than incurring severe hypoglycemic episodes known to be associated with acute and chronic cardiovascular complications [3-5]. The seminal Diabetes Control and Complications Trial (DCCT) clearly demonstrated that intensive treatment in persons with T1DM resulted in increased rates of severe hypoglycemia compared to those less well controlled when expressed in terms of glycated hemoglobin [6]. The hypothesis that abnormally high daily glucose fluctuation, between peaks and nadirs, is also associated with an increased frequency of hypoglycemic episodes [7,8] has been confirmed in both observational and interventional studies [9-14] and mathematically modelised by Rodbard [15]. Consequently, from a “glucocentric” viewpoint, the therapeutic targets in the management of persons with type 1 diabetes should include the ambient hyperglycemia, the time in range [16-20], short-term glycemic variability [21-23] and the threshold for hypoglycemia [24,25]. Although it is highly likely that the mean daily glucose concentrations and glycemic variability are the two main explanatory factors that contribute to an increased risk of hypoglycemia, their respective contribution remains to be adequately investigated. The present observational and retrospective study in a population of type 1 diabetes undergoing continuous glucose monitoring (CGM) aims to determine the relative priority of the mean daily glucose (MDG) concentration and glycemic variability (%CV) to the time spent below 3.9 and 3.0 mmol/L [17-20] representing hypoglycemia.

## Research design and methods

### *Study design and participants*

After an initial screening procedure among a population of 163 persons with T1 DM who underwent a 3- day blinded CGM, a total of 100 persons were entered into the study, of which 88 were on multiple daily insulin injections and only 12 on continuous subcutaneous

insulin infusion (CSII). The relative low percentage of subjects treated with CSII is simply due to the fact that the study was conducted between 2006 and 2012, when CSII were less used than today. In all patients treated with multiple insulin injections, the basal insulin was glargine U100 administered prior to the evening meal. Pregnant patients and those less than 20 years of age or who had experienced a recent illness or had been treated with steroids during the 3-month period preceding the investigation were excluded. All participants (65 men and 35 women) attended the outpatient clinic of the University Hospital of Montpellier (France) for greater than 3 years with a diabetes duration of 5 years or more (mean duration of diabetes = 28 years). In addition their respective insulin treatments were stable for a minimum of 3 months prior to the investigation. Continuous glycemic monitoring (CGM technology) was conducted on an ambulatory basis over a period of 3 days. Patients were also excluded from the final analysis if unexpected disruption in the glucose monitoring occurred, insufficient number of capillary blood tests or inappropriate calibrations. As recommended by the manufacturer of the CGM (the second generation Minimed System, Medtronic, Northridge, CA) four times daily finger stick determinations were performed on capillary blood samples. An acceptable calibration was based on an accuracy criterion defined by a correlation coefficient > 0.79 between paired readings. As mentioned above, all glycemic profiles were monitored on an ambulatory basis and all sensor insertions of CGM systems were performed by trained healthcare professionals at the diabetes outpatient clinic. The study was conducted in accordance with the Declaration of Helsinki each participant giving oral consent in accordance with European directive [26] that requires no approval from an ethics committee because of the non-interventional design of the study.

*Clinical investigation and laboratory determinations*

The three consecutive days of CGM avoided the weekend with the CGM sensor inserted on day 0 (before 1200h) and removed on day 3 at the same time of day. Chronic hyperglycemia (HbA1c) was assessed at baseline (study day 0) using a high-performance liquid chromatography assay [27] (Menarini Diagnostics; Florence, Italy).

***Analysis of the data from the CGM***

The data recorded on the same day as the glucose sensor for GGM was inserted were excluded from the analysis in order to avoid any bias due to insufficient glucose stabilization between the sensor and the interstitial fluid during the first 24 hours after insertion of the device. Based on two validated 24-h glycemic profiles (at 5-min time intervals) on study days 1 and 2 the total mean daily glucose exposure (MDG), short-term glycemic variability (%CV) and the presence of hypoglycemia (both symptomatic and asymptomatic) were assessed plus the cumulative time spent below three glycemic thresholds: 3.0, 3.45 and 3.9 mmol/L. As 100 patients were included in the present study and as two 24-h glycemic profiles per patient were performed, 200 glycemic profiles were suitable for analysis. Coefficients of variation for glucose (%CV) expressed as percentages were derived from the following computation: ([SD around the 24–h mean glucose value]/[24-h mean glucose]) x 100. In accordance with our own findings [11] the International Consensus on the use of CGM has now adopted the %CV as a reference to separate stable from labile diabetes [17]. The %CV has the main advantage of being the simplest metrics for assessing the short-term within-day glucose variability and secondly needs not to be adjusted for the mean daily glucose value. Due to its characteristics [28], the LBGI was not used in the present study as this metrics is necessarily highly correlated with the percentage of hypoglycemia [29] and, therefore, is more a marker to evaluate the risk of hypoglycemia than a potential causative factor for explaining the occurrence of hypoglycemic episodes. According to the recommendations of the International Hypoglycaemia Study Group [24], we consider that glucose concentration levels < 3.0 mmol/L detected by the CGM unequivocally indicate the presence of a clinical hypoglycemia. However, a glucose value < 3.9 mmol/L serves as an alert threshold when determinations are made on plasma venous samples [25]. As there are many uncertainties concerning the agreement between plasma venous glucose values and those recorded by the CGM, we decided to determine the times spent below 3.0 and 3.9 mmol/L with an intermediate glucose threshold set at 3.45 mmol/L, to indicate the presence/absence of

hypoglycemia. The time spent below the selected glucose thresholds was only recorded when the duration exceeded 15 minutes, i.e. three consecutive measurements at a 5-min interval.

**Statistical analysis**

For descriptive analysis, variables were expressed as mean ± SD or median (interquartile range, IQR) and comparisons between groups were made using either the Student's t test or the rank test of Wilcoxon-Mann-Whitney according to whether the data were normally distributed or not.

The statistical analysis was further oriented toward the goodness of fit for identifying and investigating the contributions of the independent (explanatory or predictor) variables (Xis) that can explain or predict the time spent below the three different selected glucose thresholds (dependent or outcome variables) referenced to as Ys. As the time spent below the thresholds was computed over a 24-h time interval all parameters recorded throughout the same period (the 24-h mean glucose concentration, within-day glucose variability and the daily insulin doses injected) were selected as Xis. This preliminary list was completed by 2 additional variables: the age and body mass index (BMI) because both can play a potential role.

A univariate analysis was conducted by calculating the simple linear regression between the dependent variables (Ys) and each potential explanatory variable (Xi). This statistical procedure was used for removing the independent variables that did not enter the model. Statistical significances given as p values were calculated after the time spent below glucose thresholds (normally expressed as percentage from 0 to 100%) had been converted into arcsin(square root of Y) [30] .This transformation was applied to the Ys in order to obtain an underlying distribution in agreement with the model linearity assumption. In addition the calculations used linear mixed-effect models because 2 values of Ys were obtained in each patient on two consecutive days of glucose monitoring. The relationship between the Ys and

Xis was expressed as a linear simple regression function Y = βi Xi + α, in which each partial regression coefficient (βi□□was an estimate of the relationship between Y and one given Xi. To reflect the initial units (Y expressed as percentages) the βi coefficients were transformed back to proportions and then expressed as unitless standardized coefficients that provide indications of relative importance of the explanatory variables (Xi) in determining the value of the dependent variable (Y).

In order to estimate the respective influence of each remaining Xi variable upon the dependent variable Y, a sensitivity analysis using an arborescent regression (Classification And Regression Tree, CART) [31] was performed. The methodology of this approach consisted to include all potential explanatory variables at the top of the regression tree and to sequentially select those with the best splitting for establishing a hierarchy permitting to predict their role as primary or secondary key players in the expression of the dependent variable Y. During the first step of this top-down approach the data of the independent variable that showed the best sensitivity were separated into 2 homogeneous subsamples with a cut-off (a node) value that served via a pruning procedure to either reject or maintain the data exhibiting a poor or high predictive value, respectively. The latter subsample with the highest predictive value was further submitted to the same procedure of splitting into 2 subsamples, which ended when the independent variable showed its lowest sensitivity.

To gain further insight into the best fit between Y and each Xi value entering the model the Ys were transformed into natural logarithms. The relationships (rearranged as increasing or decreasing simple exponential curves as appropriate after reverse transformation of the ordinate scale of natural logarithms) were statistically tested between dependent and independent variables by using the coefficients of correlations (r values). Comparisons between r values were made after conversion into their corresponding values of Fisher ‘s z.

Finally in the subset of 24-h glycemic profiles exhibiting mean daily glucose concentrations ≤7.8mmo/L that correspond to eHbA1c levels <6.5% (48 mmol/mol) [32], i.e. to a near

normal glycemic control [33], the time spent below 3.0 mmol/L was divided into tertiles for further statistical comparisons between medians and IQR using the rank test of Wilcoxon-Mann-Whitney for unpaired asymmetrically distributed data.

Analyses were performed with the R package, version 3.5.0 (The Foundation for Statistical Computing [www.r-project.org])

## Results

### *Demographic, clinical and laboratory characteristics of the patients at the time of enrollment in the study*

In the population considered as a whole (100 patients, and 200 glycemic profiles) means of the main parameters (± SD and range) are described as follows: HbA1c = 8.27% (67 mmol/mol) ± 0.99% (10.9 mmol/mol), range: 5.3 to 10.9% (34.3 to 95.9 mmol/mol), n =100; averaged mean daily glucose concentrations = 9.0 ± 2.4 mmol/L, range: 4.4 to 17.8 mmol/L, n= 200; %CV = 37.9% ± 11.5%, range: 82.0 to 94.8%, n =200; daily insulin doses = 0.67 ± 0.20 units/kg/day, range = 0.37 to 1.21 units/kg/day, n=100; age = 55.7 ± 13.1 years, range = 20.0 to 83.0 years, n= 100; BMI : 24.8 ± 3.1 kg/$m^2$, range = 19.1 to 34.9 kg/$m^2$, n =100.

### *Comparison of glycemic profiles and clinical characteristics according to whether amounts of time were spent or not below the glucose thresholds*

The two hundred 24-h glycemic profiles recorded in the 100 participants were divided into 2 categories according to whether no time or a positive amount of time was spent below the selected glucose thresholds of 3.0, 3.45 and 3.9 mmol/L (table 1). As expected, the number of glycemic profiles without any time spent below the selected thresholds was smaller when the glucose threshold was set at 3.0 mmol/L rather than at 3.9 mmol/L. Mean daily glucose concentration and %CV were significantly lower and higher, respectively, when glycemic profiles with glucose values below the thresholds were compared with those with no time spent below each of the three glucose thresholds. Daily insulin doses, age and body mass

index (BMI) did not differ across the different groups irrespective of the presence/absence of time spent below the glucose thresholds.

***Relationships between the times spent below the different thresholds (Y) and the independent variables (Xi)***

When the time spent below the selected thresholds (Y) was expressed as its arcsine transformation, i.e. the arcsin $\sqrt{Y}$, the univariate mixed regression analysis showed strong positive and negative relationships ($p< 0.001$) with the %CV and the mean daily glucose concentration (MDG), respectively. The unitless standardized partial coefficients of regression (βi) for the thresholds of 3.9, 3.45 and 3.0 mmol/L were positive for the %CV ($\beta_1$ = + 1.31, + 1.08 and + 0.75, respectively) and negative for MDG ($\beta_2$ = - 1.07, - 0.58 and - 0.35, respectively) indicating that the time spent below the selected glucose threshold increased with increasing %CV and decreasing mean glucose concentrations, respectively. In contrast, the remaining independent variables, i.e. the daily insulin doses, age and BMI did not correlate with the time spent below the different glucose thresholds. When the thresholds were set at 3.9, 3.45 and 3.0 mmol/L the respective p values were of 0.92, 0.91 and 0.60 for daily insulin doses; of 0.25, 0.16 and 0.24 for age and finally of 0.17; 0.13 and 0.07 for BMI. As a consequence the latter 3 variables were no longer considered to be explanatory, and were thus removed from the model of statistical analysis.

***Classification and regression trees***

As the statistical significances of %CV and mean daily glucose are both highly significant ($P<0.001$) we used the CART method (Classification and Regression Tree) to decipher whether one of them is more significant than the other. Different results were obtained when the three selected thresholds were tested (figure 1). At 3.9 mmol/L, the MDG was the first explanatory variable but when the glucose thresholds were set at 3.0 and 3.45 mmol/L the % CV appeared as the primary factor associated with higher risk of hypoglycemia (figure 1). When the threshold was set at 3.0 mmol/L, the %CV was the first variable that entered the

top of the regression tree. The first node of %CV for partitioning the tree was found at 47.3%. The subsample with the %CV below 47.3% was subsequently pruned from the regression tree and in this subsample the mean terminal value of the time spent below 3.0 mmol/L was of 1.7%. The subsample with the %CV ≥ 47.3% was retained for a further splitting. As expected, the second explanatory variable entering the regression tree was the MDG with a splitting node at 6.8 mmol/L. The subsamples with a MDG ≥ or < 6.8 mmol/L ended with mean time durations spent below 3.0 mmol/L, which were computed at 6.8 and 26.0 %, respectively, as indicated at the bottom of the terminal branches.

***Exponential relationships between the time spent below 3.0 mmol/L and the mean daily glucose or the %CV.***

The results are illustrated in figures 2a,b. The relationship between the percentages of time spent below 54 mg/dL (3.0 mmol/L) (Y) and the MDG (X, mg/dL) was described by a simple decreasing exponential curve: $Y = 23.66\ e^{-0.009x}$; r = - 0.358, p < 0.001. When Y was plotted against the % CV (X) the relationship was represented by a simple increasing exponential curve: $Y = 0.93\ e^{0.043x}$, r = 0.509, p < 0.001. The comparison between the 2 coefficients of correlation did not show any significant difference by testing the corresponding z values after Fisher's transformation = 1.87, p = 0.065, even though the r value for the %CV seemed to be slightly better than that for the MDG.

***Time spent below 3.0 mmol/L after dividing the %CV into tertiles in the subset selected by mean glucose values less than 7.8 mmol/L***

Among the 200 daily glycemic profiles, 65 exhibited mean glucose concentrations ≤ 7.8 mmol/L. After dividing this subset by %CV the following tertiles were selected: 1 (%CV <34%, n = 21); 2 (%CV between 34 and 44.1%, n = 22); and 3 (%CV >44.1%, n = 22). As illustrated in figure 3 percentages of time spent below 3.0 mmol/L (medians [IQR]) were statistically greater in the upper tertile 3 (15.6% [IQR= 20.5%]) when compared with the two others:

p<0.001 vs tertile 1 (0.0 % [IQR= 2.7%]) and p<0.01 vs tertile 2 (3.1% [IQR= 5.5%]). No difference was found between tertiles 1 and 2.

## Discussion

Several key messages can be drawn from the present study. Firstly, the two main factors for predicting the risk of hypoglycemia in persons with type 1 diabetes are low or near normal daily glucose levels and abnormally high glucose fluctuations from peaks to nadirs. Secondly the role of these two factors was found to be approximately equivalent across the range of glucose thresholds from 3.9 to 3.0 mmol/L even though excessive within-day glucose fluctuations appeared to be increasingly involved in predicting the risk of hypoglycemic episodes and precipitating their onset with decreasing the glucose threshold used for defining hypoglycemia. In addition the coefficient of correlation of the exponential curve depicting the relationship between the time spent below 3.0 mmol/L and the %CV was found to be greater than that for the mean daily glucose value as explanatory variable even though the differences were not statistically significant. Similar findings derived from a less sophisticated mathematical analysis were observed for the %CV and were reported recently at the 2018 meeting of the American Diabetes Association [34]. Nevertheless, all these results reinforce the opinion that besides achieving near normal glycemia for preventing the development or progression of micro and macrovascular complications [6,35-38], it is crucial to try to reduce as much as possible the magnitude of glucose swings in order to limit the risk of hypoglycemia, a major challenge for improving the quality of life of persons with type 1 diabetes [7-14]. This position is supported by two additional findings. Firstly in all groups the averaged %CV were below 36% (the limit that separates stable from labile diabetes [11,17]) when the patients did not spent any time below the selected thresholds, whatever the values chosen from 3.9 to 3.0 mmol/L. By contrast, the averaged %CV was always above 36% when the patients spent a positive amount of time above the aforementioned glucose thresholds. Secondly the computation by tertiles of %CV in the subset with near normal mean daily glucose values showed that the amount of time spent below 3.0 mmol/L was

rarely positive when the %CV was less than 34%. Therefore, maintaining the %CV below this threshold should be a suitable recommendation for limiting the risk of hypoglycemia when the mean daily glucose concentration is stabilized and maintained below 7.8 mmol/L, i.e. a value that corresponds to a near normal glucose exposure [32,33]. Even though the two thresholds of 36 and 34% are very close their meaning is quite different. A %CV above 36% is synonymous of frequent hypoglycemic episodes (labile diabetes) regardless of mean daily glucose concentrations whereas achieving a %CV below 34% ensures a very low risk of hypoglycemia when a tight glycemic control is obtained in terms of overall glucose exposure. Until recently only a limited number of people with type 1 diabetes concomitantly attained such targets of low %CV and near normal mean daily glucose concentration with conventional insulin treatments consisting either of daily multi-injections or even continuous subcutaneous insulin infusion with pumps [39]. However, the expanded use of novel devices for continuous glucose monitoring [17,40,41] or the ceaseless progression towards the implementation of more and more sophisticated systems for closed-loop insulin delivery [42] raise both promising expectations for improving the glucose homeostasis in persons with type 1 diabetes. Even though it is highly likely that the reduction in short-term glycemic variability is one of the key player for the diminution in the incidence of hypoglycemia, the observation of a strong relationship between the %CV and the time spent below different glucose thresholds does not permit to distinguish whether glucose variability is the cause or the consequence with regard to the time spent below the recommended target glycemic range usually set between 3.9 and 10 mmol/L [17,18,20]. It should be noted that the present study was conducted in patients who were carefully instructed to ingest moderate amounts of refined carbohydrates in order to prevent excessive glycemic rebounds during post-hypoglycemic periods and thus to avoid any subsequent additional deterioration of glucose variability. Furthermore as the CGM data were masked to the patients throughout the entire monitoring period, all asymptomatic hypoglycemia were not subject to therapeutic interventional measures of correction in the absence of any warning signs. Consequently there are many reasons to consider that excessive glucose variability is more a causative

factor of hypoglycemia than its consequence. This study has some limitations due to its observational design, the short duration of the study period albeit all CGM were conducted on an ambulatory basis, and finally the potential inaccuracy of sensors when glucose values are within the lower range of the CGM.

In conclusion and addressing the question raised in the title of this article it appears that the excess of short-term glycemic variability assessed from the within-day coefficient of variation for glucose is at least equivalent to and perhaps slightly more important than the mean daily glucose level to prevent the risk of hypoglycemia, especially when the threshold of hypoglycemia is set at its lower level of 3.0 mmol/L. In addition striving to achieve a %CV below 34% in patients who have already a satisfactory glycemic control in terms of chronic glucose exposure (mean daily glucose concentration ≤7.8 mmol/L) should be one of the main objectives in the management of type 1 diabetes.

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Authors' contributions : LM participated in the study design, data collection and interpretation and writing of the manuscript. AW, CC, ER and DO participated equally to the study design, data interpretation and critical revision of the manuscript. NM carried out the statistical analysis. LM is the guarantor of this work and, as such, had full access to all the data and their analyses.

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| Thresholds set at | 3.0 mmol/L | | 3.45 mmol/L | | 3.9 mmol/L | |
|---|---|---|---|---|---|---|
| | No | Yes | No | Yes | No | Yes |
| N° of glycemic profiles | 120 | 80 | 100 | 100 | 71 | 129 |
| Age (years) | 56±14 | 53±12 | 56±14 | 53±12 | 57±14 | 54±12 |
| BMI (kg/m$^2$) | 24.5±3.0 | 25.5±2.9 | 24.6±3.1 | 25.2±2.9 | 24.7±3.1 | 25.0±3.0 |
| MDG (mmol/L) | 9.8±2.4* | 7.9±2.0 | 10±2.4* | 8.0±2.0 | 10.4±2.3* | 8.2±2.2 |
| %CV for glucose (%) | 33±9* | 44±11 | 32±9* | 43±11 | 31±9* | 42±11 |
| Insulin dose (units/kg/day) | 0.66±0.20 | 0.68±0.19 | 0.66±0.20 | 0.67±0.20 | 0.67±0.20 | 0.66±0.20 |

*$p < 0.001$

Table 1: Glycemic profiles were separated into 2 groups according to whether they exhibit (yes) or not (no) a significant duration of time (>15 min) spent below different thresholds i.e. 3.0, 3.45 and 3.9 mmol/L. Statistical comparisons between glycemic profiles (referenced to as yes or no) were only indicated when p values < 0.001.

Legends of figures

Figure 1: Classification and regression tree (CART) procedure.

The respective influences of the potential explanatory variables (the mean daily glucose concentration and the %CV) upon the dependent variable (the time spent below the selected thresholds: 3.9, 3.45 and 3.0 mmol/L) are estimated using the CART. The subsamples splitted from the threshold values (nodes of the open circles) are considered to be the best true (right branch) or false predictors (left branch) for the risk of hypoglycemia assessed from the percentage of time spent below 3.9, 3.45 and 3.0 mmol/L. For instance a $Y_{end}$ value of 26.0 at the end of the right branch of the regression tree (threshold <3.0 mmol/L) means that after a true stepwise splitting that selected the 1$^{st}$ (%CV) and 2$^{nd}$ (MDG) line explanatory variables the averaged percentage of time spent below 3.0 mmol/L is of 26.0 %. When these explanatory variables are not truly selected the final percentage is only of 1.7 %. In summary, the right itinerary that has selected the %CV and the MDG as first and second explanatory variables, respectively, at thresholds of 47.3% for the %CV and 6.8 mmol/L for the MDG, corresponds to the best selection with the highest sensitivity (26%).

Figure 2: Simple exponential relationships

The time spent below 3.0 mmol/L is plotted against the mean daily glucose concentration (figure 2a) or the coefficient of variation for glucose (figure 2b).

Figure 3: Percentages of time spent below 3.0 mmol/L

The data of %CV were divided into tertiles in the subset of 65 daily glycemic profiles exhibiting mean glucose concentrations ≤7.8 mmol/L. Data distributions around medians are expressed as interquartile ranges (IQR illustrated by boxes), 90$^{th}$ percentiles (illustrated by vertical lines and their upper and lower limits) and ranges from minimum to maximum.

Figure 1

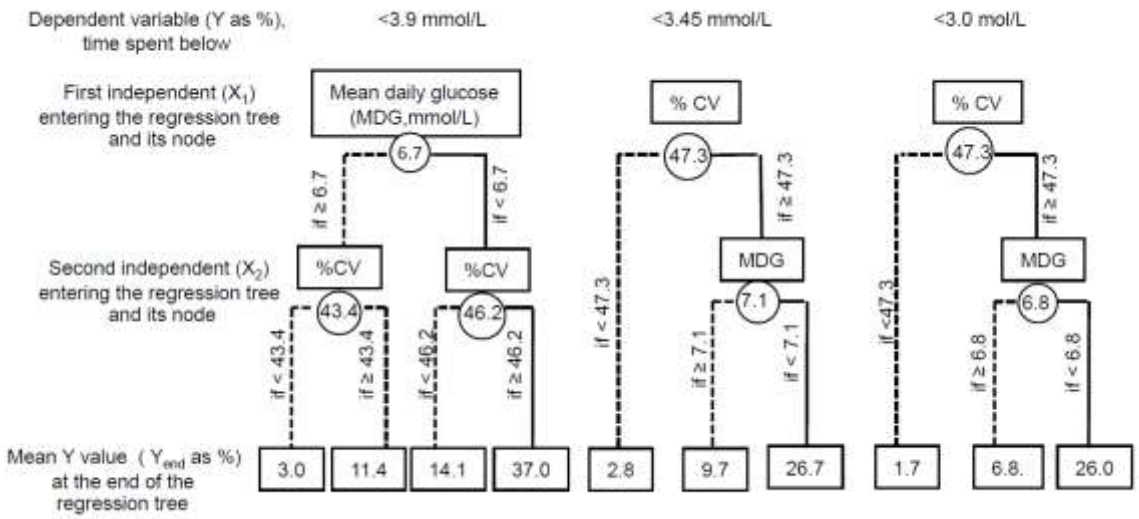



Figure 2a

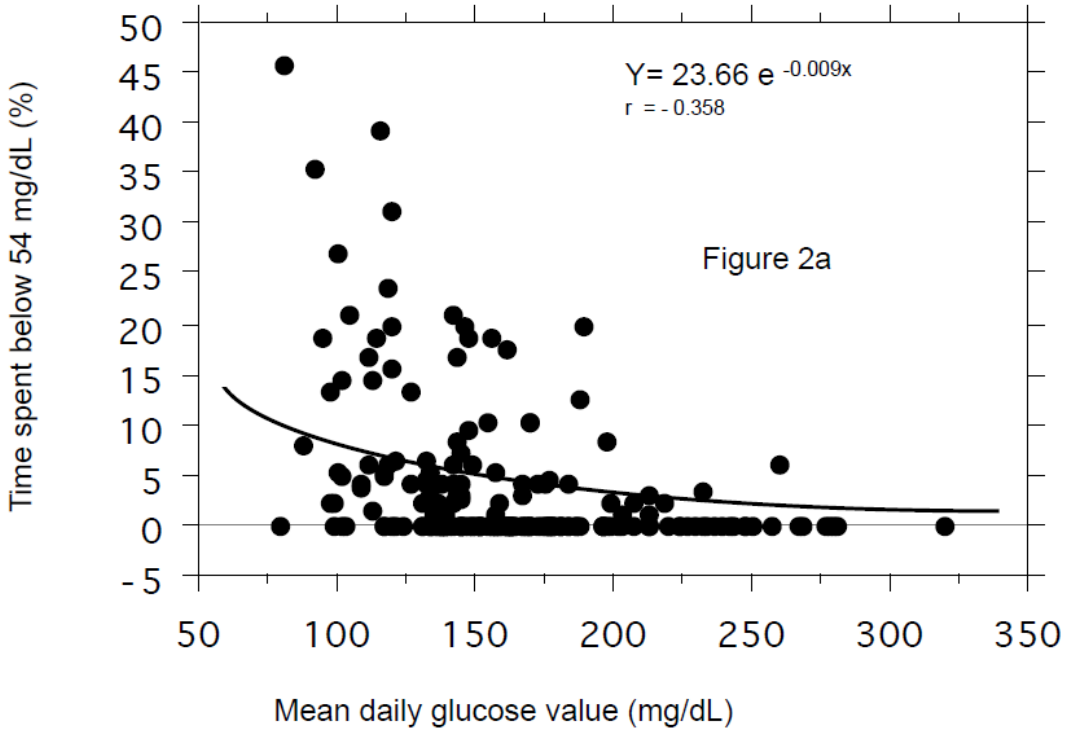


Figure 2b

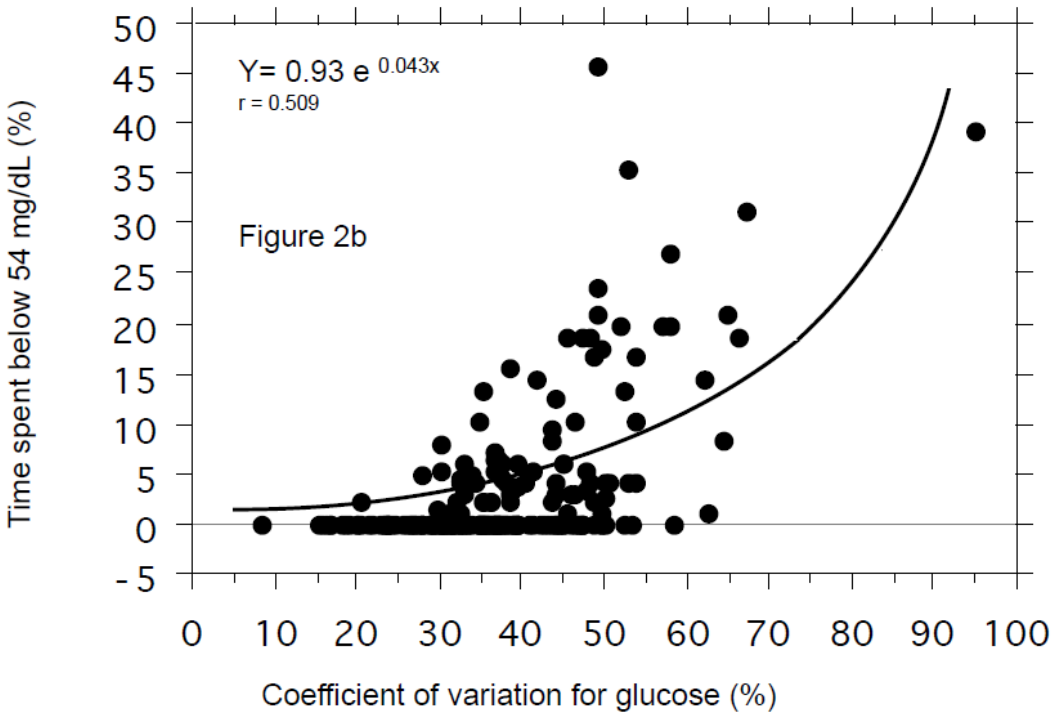
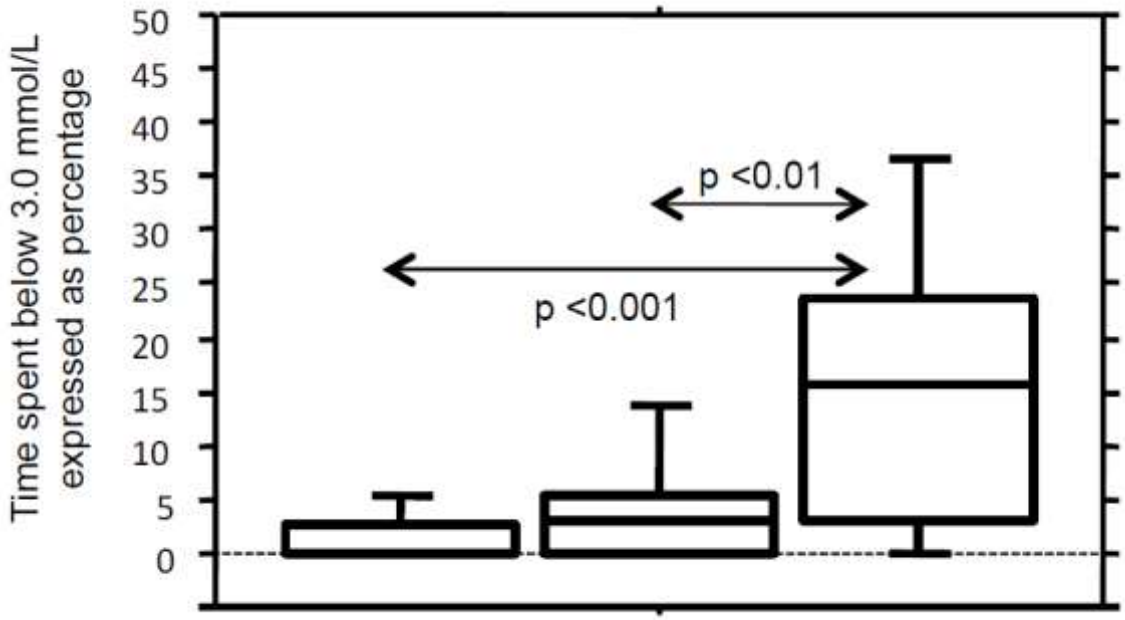

Y= 0.93 e 0.043x
r = 0.509
Figure 2b
Time spent below 54 mg/dL (%)
Coefficient of variation for glucose (%)
50
45
40
35
30
25
20
15
10
5
0
- 5
0
10
20
30
40
50
60
70
80
90
100

Figure 3




| Tertile with %CV | <34% | 34- 44.1% | >44.1% |
|---|---|---|---|
| Number of profiles | 21 | 22 | 22 |
| Median | 0.0 | 3.1 | 15.6 |
| [IQR] | [2.7] | [5.5] | [20.5] |
| Range | 0.0 – 8.0 | 0.0 -15.6 | 0.0 - 45.8 |