

# **Role of continuous glucose monitoring in the pediatric intensive care unit**

Doctoral thesis

**Dr. Gábor Marics**

Semmelweis University  
Doctoral School of Clinical Medicine



Supervisor: Dr. Péter Tóth-Hejn, Ph.D., associate professor

Official reviewers: Dr. Nóra Hosszúfalusi, M.D., Ph.D., associate professor  
Dr. Gyula Tálosi, M.D., Ph.D., associate professor

Head of the Comprehensive Exam Committee:  
Dr. Zsolt Iványi, M.D., Ph.D., associate professor

Members of the Comprehensive Exam Committee:  
Dr. Katalin Darvas, M.D., Ph.D., associate professor  
Dr. Levente Kovács, Ph.D., associate professor

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## **Introduction**

It has long been known that in severe acute conditions the blood glucose level increases. In the 1930s hyperglycemia-associated glucosuria accompanying myocardial infarction was already a known phenomenon, although in accordance with the classical hypothesis of that era it was thought to be a necessary physiological response. Subsequent research revealed that hyperglycemia during acute illness had worsened the clinical outcome. The latter results debated the beneficial effects of the so called stress hyperglycemia, and therefore the original concept that critical illness hyperglycemia was a practical adaptation mechanism to meet the increased substrate demand was re-evaluated.

Studies aiming for “target blood glucose ranges” appeared around the millennium among critically ill patients. In this field the publication by Van den Berghe in 2001 was definitely the milestone one. The randomized controlled study recruited more than a thousand mechanically ventilated surgical critical care patients and it found a 34% reduction in mortality among the tight glycemic control (TGC) group (target range: 4.5–6.6 mmol/l) compared to the conventional group (target range: < 12.0 mmol/l). Subsequent studies revealed that not only hyperglycemia, but hypoglycemia, the most important side effect of intensive insulin therapy (IIT), was also independently associated with mortality. Considering these risks the current adult and pediatric guidelines support the conventional critical care insulin protocols, which are regarded generally safer in the intensive care setting, and therefore the implementation of insulin therapy is only recommended if blood glucose exceeds 10-12 mmol/l.

By the application of conventional blood glucose measurements significant hypo-, and hyperglycemic episodes may remain unrecognized; however continuous monitoring could enable better glycemic control, more accurate insulin therapy and could promote the optimal utilization of the benefits of IIT.

The continuous glucose monitoring (CGM) system, which measures the interstitial glucose concentration, is an established care tool for diabetic patients. For the evaluation of its usability in the

intensive care setting research has been taking place since the early 2000s. The CGM system contains three main elements: the sensor, the monitor and the transmitter. The sensor is a platinum electrode impregnated with glucose oxidase, which is implanted into the subcutaneous tissue with a special implanter tool. The enzymatic reaction generates a current signal, which is proportionate to the interstitial glucose concentration. The transmitter maintains the connection between the sensor and the monitor. In the CGM system (Medtronic<sup>®</sup> Guardian<sup>®</sup> Real Time) applied by us, the monitor is continuously processing the glucose signal, results are all stored and the screen gets updated every 5 minutes. The system has to be calibrated at least every 12 hours using reference blood glucose values. Different forms of shock, circulatory and respiratory support need are common in the ICU setting, which result in reduction of tissue perfusion, therefore it has been debatable whether CGM could be applied in the ICU with appropriate accuracy. Current practice has been based on an international recommendation from 2009, which does not support the independent CGM-guided decision making among critically ill patients.

Continuous glucose signaling opens up a new perspective for research on ICU-related hyperglycemia. It is known from literature data that certain glucose variability (GV) parameters are associated with mortality. Although the research on GV is still in its infancy, it is important to point out that its parameters are complex and sophisticated, giving the possibility to answer specific and more detailed questions. The calculation of the parameters is rather complicated though, therefore most studies have not fully utilized the potential of GV.

## **Aims**

### **1. Creation of a pediatric intensive care database to facilitate CGM-related data process**

Prior to setting up this clinical study it became necessary to develop a well-structured database in order to promote our research mainly

by supporting the clinical data management and enabling the easy access to clinical data. Giving that a suitable Hungarian user-interface was not available at the time, our first task was to design and create a database of such.

## **2. Determination of the accuracy of CGM in pediatric intensive care unit**

Although in 2012 there were already some published data available on the accuracy of CGM, for the purposes of this study it was felt essential to determine the accuracy of CGM in our subpopulation, before looking into more specialized research topics.

## **3. Evaluation of the effect of tissue hypoperfusion on the accuracy of CGM**

Every clinical recommendation -either for diabetic or intensive care populations- refers to blood glucose levels. In contrast, CGM measures the interstitial glucose concentration. The glucose concentrations differ in these two compartments; and the time constant is roughly 15 minutes between them. By incorporating this knowledge, previous studies found CGM a useful monitoring tool even in the intensive care unit. However, it remains an important question whether and how tissue hypoperfusion under intensive care circumstances may influence on the accuracy of CGM.

## **4. CGM as a clinical diagnostic tool**

In several emergency situations the kinetic change of glucose could help to make the proper diagnosis. During our study period we aimed to initiate a CGM examination in every pediatric patient with symptoms of glucose regulation disorders. The thesis describes two cases with hypoglycemic episodes where CGM gave indispensable support.

## **5. Development of glycemic variability analyzer program**

The CGM system supplies a continuous glucose signal, which could reveal new prospects for GV. The calculations of these parameters are considerably complicated and time-consuming. To solve this

problem and to support our research we have developed a program for GV calculation (Glycemic Variability Analyzer Program, GVAP).

## **Methods**

### **1. Creation of a pediatric intensive care database to facilitate CGM-related data process**

For the development of our database we used MS Access 2010. During the design phase it was a major consideration that the program should be able to record the most important intensive care variables on top of the basic demographic data. During intensive care monitoring excessive data are recorded. In our dataset we grouped these parameters together in different spreadsheets, where a separate table contained data related to patient care, medication, ventilation, etc. The data related to tissue hypoperfusion were calculated based on blood gas analysis. The major advantage of using separate datasheets for distinct variables is that one can access the spreadsheets in a very simple way if specific queries arise. This can increase the effectivity of the current study and of any other investigation to be carried out in the same cohort.

### **2. Determination of the accuracy of CGM in pediatric intensive care unit**

For analyzing the accuracy of CGM we compared the glucose measurement provided by CGM to the blood glucose level, measured concurrently by the reference method. In our study blood gas analyzer or point of care blood glucose meter (POC) (GEM 3000 Premier™, Instrumentation Laboratory®; DCONT Ideal®, 77 Elektronika®) were used as reference.

We assessed the clinical accuracy of CGM by Clarke's Error Grid Analysis. Pearson correlation analysis and Bland-Altman analysis were performed to evaluate the mathematical precision of CGM.

Study population: 38 patients, 40 CGM recordings, mean age (range): 1.3 (0-18) year; gender: 10 female; 28 male; average time

spent in intensive care unit (range): 21 (1-80) days; 32/38 patients needed invasive respiratory support, 11/38 circulatory support (noradrenalin, adrenalin or dopamin). The most common pathology requiring ICU admission was respiratory failure. The normality was evaluated by Kolmogorov–Smirnov test. Programs used during the study were the following, MATLAB® 2010b and STATISTICA 8.

### **3. Evaluation of the effect of tissue hypoperfusion on the accuracy of CGM**

Blood gas analysis provides several additional laboratory parameters, which reflect on tissue hypoperfusion. In our study we examined the effects of pH, lactate, hematocrit and serum potassium on the accuracy of CGM. For these purposes we included all achieved blood gas records performed during the study period. To evaluate the effect of hypoperfusion we created specified groups for each parameter and we made comparisons with the aim to assess whether there was a statistical difference between the CGM and the reference blood glucose in the groups. Statistical method: repeated measures ANOVA. Graphical visualization: Y axis represents the mean of CGM – reference glucose concentration with its standard error of mean (SEM); X axis shows the different parameters of the specified groups.

### **4. CGM as a clinical diagnostic tool**

#### **▪ 1. case**

In the case of a female neonate admitted with persisting apnea, congenital central hypoventilation syndrome (CCHS) was confirmed in the background of the respiratory defect. Besides the apnea the investigations confirmed the presence of hypoglycemic episodes, therefore CGM measurement was initiated. The laboratory findings confirmed decreased serum cortisol and elevated insulin levels as possible etiologies for the hypoglycemia. Increased carbohydrate intake and hydrocortisone supplementation did not result in significant improvement, therefore diazoxide was added to attenuate the effect of insulin. To analyze the effect of diazoxide we

introduced a second CGM measurement protocol. For the evaluation of the effectiveness of treatment we used CGM glucose values before and after the intervention. We characterized the anti-hypoglycemic effect of diazoxide with the time spent below the target range (3.9-7.8 mmol/l), and furthermore we examined its effect on serum insulin level, as well. Wilcoxon test was used for statistical analyses and p values less than 0.05 were considered statistically significant.

▪ **2. case**

The 1.5-year old male was admitted to our department after a seizure. He was born with esophagus atresia and underwent consequential “gastric pull up” surgery with pyloromyotomy. In the background of convulsion severe hypoglycemia (<2.2 mmol/l) was found, measured by POC. We started his first CGM measurement during conventional feeding firstly to identify the hypoglycemic episodes and secondly to reveal glucose kinetics. The second CGM session was commenced during continuous maltodextrin-enriched diet, which was prescribed for the management of hypoglycemia.

**5. Development of glycemic variability analyzer program**

Our main purpose during the development process of the GVAP was to make the program capable of calculating the most common glucose variability parameters accurately and quickly in a user-friendly format. We used MATLAB<sup>®</sup> 2010b as a developing environment. The following parameters can be determined by GVAP: (1) within day GV (CONGA - Overall Net Glycemic Action); (2) inter day GV (MODD - Mean of Daily Differences); (3) average area above/below the target range (Avg. AUC-H/L); (4) average time above/below the target range in percentages (PATR/PBTR); (5) Mean Amplitude of Glycemic Excursions (MAGE avg.).

For the validation of the GVAP we used 14 (in case of MAGE 20), 48-hour long CGM curves. We used Pearson correlation analysis for CONGA, MODD, MAGE; after logarithmic transformation for Avg. AUC-H and PATR; Spearman analysis for Avg. AUC-L and

PBTR to evaluate the precision of the GVAP. We used the following reference methods: (1) Medtronic<sup>®</sup> for AUC-H/L and PATR/PBTR; (2) GlyCulator for CONGA and MODD; (3) manual validation for MAGE based on Baghurst definition.

The source code of the GVAP has been made freely available for other researchers, and moreover we tested its usability based on the provided user documentation.

## Results

### 1. Determination of the accuracy of CGM in pediatric intensive care unit (Figure 1)

We used calibration glucose values and relevant blood gas recordings to assess the accuracy of CGM (n=780). The Pearson correlation coefficient was 0.83. Based on the Bland-Altman analysis the average difference between the reference and the CGM glucose was

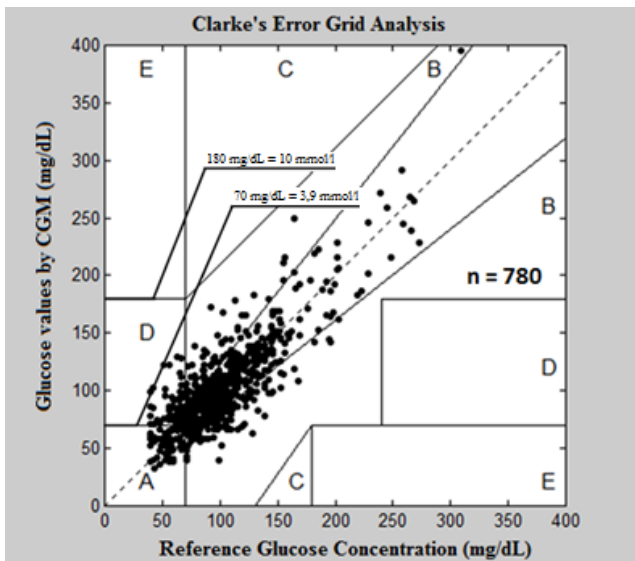


Figure 1. Clarke's Error Grid Analysis



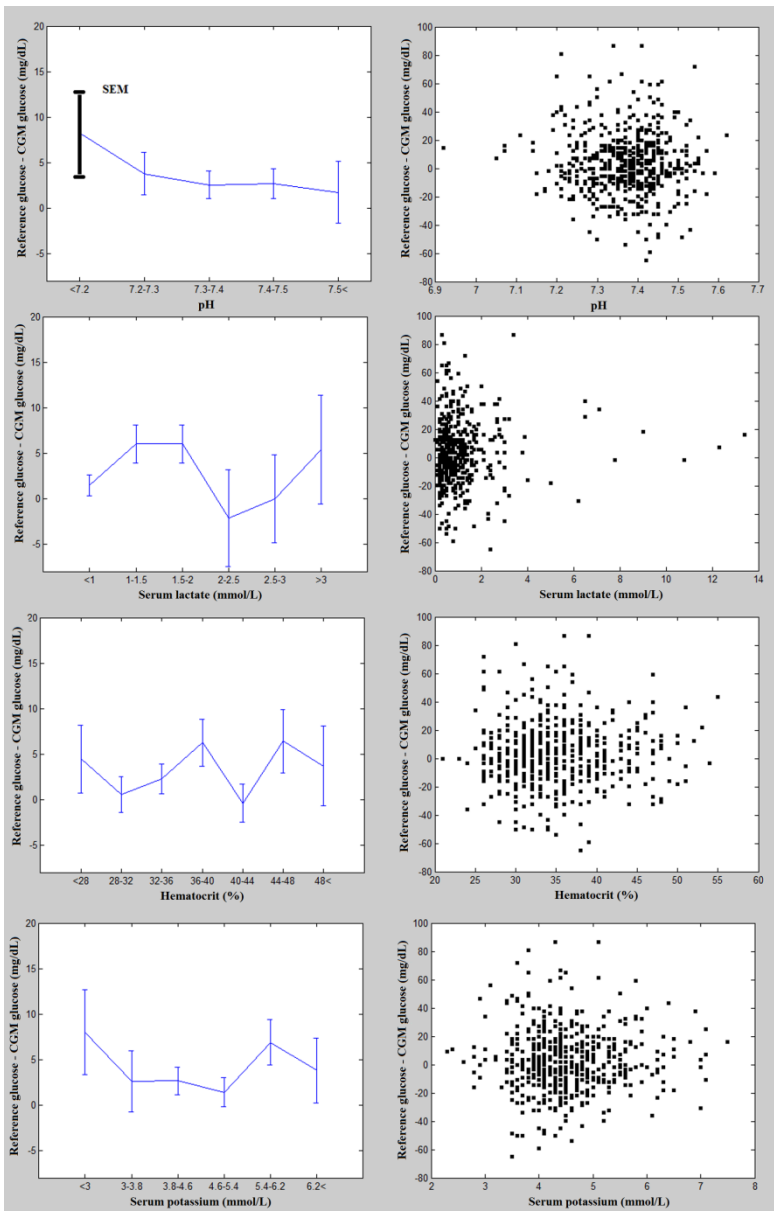
1.3 mg/dL (0.07 mmol/l). Forty-eight point pairs exceeded the 2SD limit line (2SD = 2.3 mmol/l). The clinical accuracy of the CGM system was 96% in our cohort (Clarke A and B zone). Our results are in accordance with those of the international publications.

## **2. Evaluation of the effect of tissue hypoperfusion on the accuracy of CGM (Figure 2)**

The mean differences between the CGM and the reference levels were between minus 2 and 8 mg/dL (-0.11-0.44 mmol/l) for all examined parameters. The means and the SEMs, presented on Figure 2. showed tendency with some of the parameters (e.g. pH, lactate), however statistical significance was not reached. (As the parameters did not follow normal distribution, Friedman test was used for statistical analysis.). On the right side of Figure 2. the measured values and their differences are charted. The measuring errors were not located in the extremities (severe acidosis, hyperlactatemia, severe anemia, hypo- or hyperkalemia), moreover in these ranges CGM was found to be rather accurate. Clinically significant variation was not demonstrated, not even for cases with the highest reference-CGM glucose differences based on the Clarke's analysis.

It could be inferred from the measuring principle of CGM that tissue hypoperfusion adversely affects its accuracy. Our chosen key elements were pH and lactate from the selected parameters to assess the effect of tissue hypoperfusion on CGM precision.

In acidosis and/or elevated lactate levels, characteristic for hypoperfusion, no significant interference was detected with the accuracy of the method. Our results are in keeping with previous publications that neither hypothermia nor vasopressor treatment impairs the accuracy of CGM. The scatter plots show that the measuring errors represent stochastic distribution, which refers to uncertainties of the CGM system.

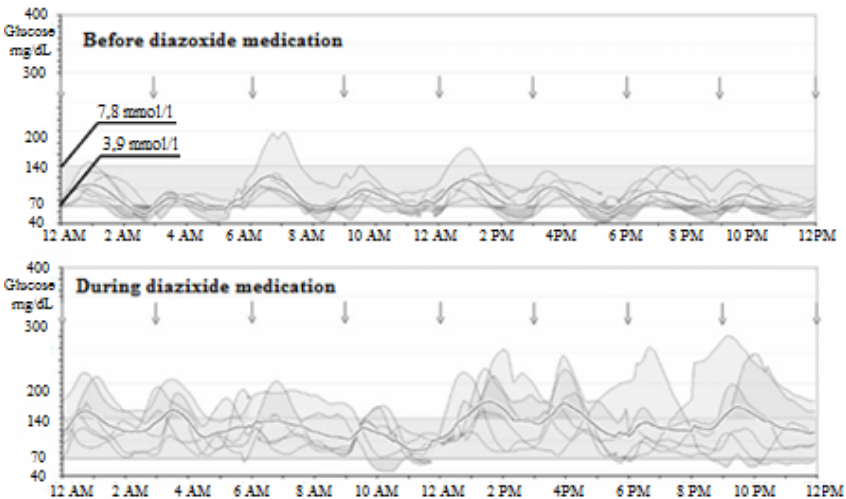


**Figure 2.** The effects of pH, lactate, hematocrit and potassium on the accuracy of CGM (glucose conversion: 18 mg/dL = 1 mmol/l)

### 3. CGM as a clinical diagnostic tool

- *1. case (Figure 3)*

In our CCHS patient CGM confirmed that the hypoglycaemia had typically manifested 90–120 minutes following the last meal and had lasted until the next feeding. The glucose levels increased significantly in response to diazoxide medication [4.6 (2.3; 10.5; median, min, max) mmol/l versus 6.4 (2.7; 15.6) mmol/l,  $p < 0.001$ ]. The time spent below the target range (3.9–7.8 mmol/l) also decreased from 29% before diazoxide to 4% during the treatment, and the previously high insulin level normalized.



**Figure 3** The effect of diazoxide on the subcutaneous glucose profile in our CCHS patient. The so-called modal day CGM curves represent the daily glucose excursions and the 6 day average values (dotted line). The arrows show the feedings

The postprandial hypoglycemia identified by CGM may have been caused by the underlying PHOX2B gene mutation. The role of abnormal functioning of this transcription factor may have central impact on the CCHS-associated hypoglycemia in several ways, such as deterioration of low glucose sensing, impaired autonomic response and increased insulin secretion.

In previously published case reports the diagnosis of CCHS was often made following hypoglycemia-associated seizures. In our case the early diagnosis, the availability of CGM and the prompt start of appropriate therapy prevented the development of further complications. We propose that CGM monitoring could help the optimization of therapy and the avoidance of complications in similar cases.

▪ **2. case (Figure 4)**

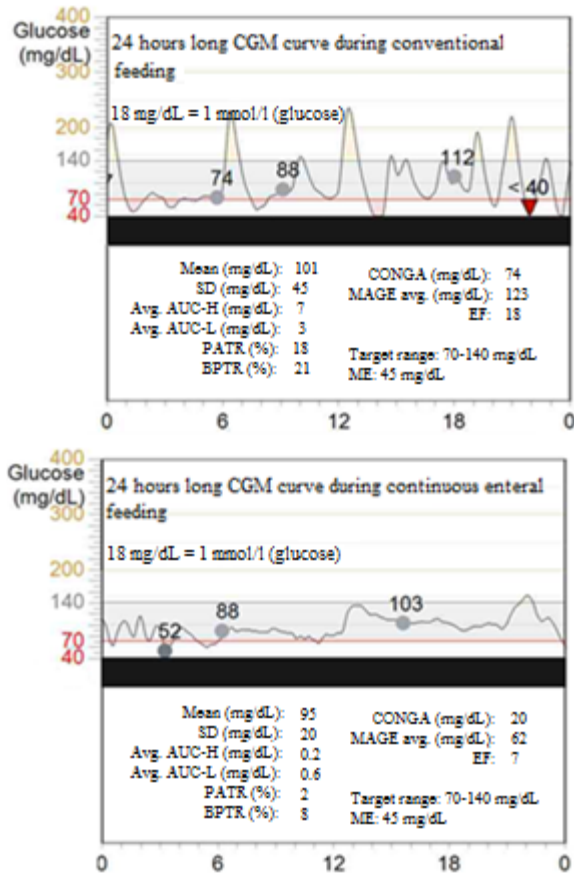
In the child with esophagus atresia and convulsion CGM measurements revealed significant hyperglycemia after meals, which were followed by hypoglycemic episodes 2-3 hours later. This rapid glucose absorption-like CGM pattern was secondary to dumping syndrome following pyloromyotomy. Continuous nasogastric enteral feeding was introduced with prolonged absorption carbohydrate (maltodextrin). As a result of dietary intervention glycemic variability reduced and postprandial hypoglycemic episodes became less frequent. Subsequent neurological impairment did not occur. This has been the first documented case of its kind, which draws the attention to dumping syndrome-associated hypoglycemia and convulsion after “gastric pull up” surgery.

**4. Development of glycemic variability analyzer program**

The correlation coefficients were above 0.99 for all examined variability parameters. The Bland-Altman analysis found mathematically significant differences (~1 mmol/l) between the results of GVAP and the reference in two cases, and the retrospective analysis confirmed manual calculation errors in the background of them.

Based on the test examiners’ reports the online accessible user manual has been well designed. With its guidance the use of GVAP could have been learned in half an hour. With the Windows® based application each run took approximately 1 minute.

As a clinical example we analyzed the effect of continuous feeding in our patient with dumping syndrome. Due to the intervention all GV parameters reduced. In this clinical case the reduction of CONGA was the most informative parameter, as CONGA reflects on the short term variability very well, which refers to the average hourly changing in glucose concentration. In this case the average hourly change was rather high during the conventional



**Figure 4.** The effect of continuous feeding on the glycemic variability .The dots are the calibration points.

feeding hourly changing in glucose concentration. In this case the average hourly change was rather high during the conventional feeding (CONGA = 4.1 mmol/l), but the continuous feeding attenuated the fluctuations (CONGA = 1.1 mmol/l).

Our study further supports that GVAP has potential research perspective in both diabetic and intensive care populations.

## **Conclusions**

1. The accuracy of CGM remains below that of the analytical measurements, blood gas analyzers and POCs; however CGM data has been found very useful for trend analysis. Our results confirm that CGM is a valuable tool for continuous measurement of glucose levels in the subcutaneous tissue in critically ill pediatric patients.
2. The accuracy of CGM is not dependent on the changes of laboratory parameters indicative of tissue hypoperfusion, thus states typical of PICU patients with disturbed microcirculation do not limit its suitability.
3. CGM supports practitioners to make the correct diagnosis and initiate appropriate therapy by providing continuous kinetic reports; moreover in special circumstances CGM can contribute to the better understanding of the underlying pathophysiology and the establishment of diagnostic algorithms.
4. The autonomic nervous system plays a complex role in CCHS-associated hypoglycemia. CGM played an essential role in the description of this phenomenon in our case.
5. After “gastric pull up” surgery hypoglycemic episodes and convulsions may develop secondary to dumping syndrome. CGM proved to be a valuable tool for the identification of the underlying pathomechanism and furthermore for the prevention of convulsions in the presented case.
6. We developed a user friendly program (GVAP) for the analysis of glycemic variability; which has been made freely accessible for

researchers. With its usage one can assess continuous glucose monitoring curves easily and calculate the most common GV parameters accurately. We hope that our program can promote the exploration of the impact of GV in the intensive care setting.

## **Bibliography of the candidate's publications**

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