

ORIGINAL PAPER

# The continuous glucose monitoring system correlates poorly with the glucose infusion rate

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## ABSTRACT

**Introduction:** Increased risk of death and morbidities have been observed among infants with very low birth weight (VLBW) who develop hyperglycaemia. The mechanisms of hyperglycaemia are multifactorial, and it has been speculated that one of the most common causes is a high glucose infusion rate (GIR). There is insufficient data concerning the relationship between GIR and glycaemia with the use of a continuous glucose monitoring system. Obtaining data on this connection can shed light on the pathophysiology of hyperglycaemia in VLBW infants. The aim of study was to evaluate the relationship between glucose delivery and the risk of hyperglycaemia in VLBW infants.

**Material and methods:** Data from a total of 74 patients who participated in this continuous glucose monitoring study during their first week of life were analysed retrospectively. The median interstitial glucose concentration (IGC) was calculated for each patient, on each day, and the values were used to divide the patients into quartiles. The median gestational age was 28 weeks (interquartile range 27–31), mean birth weight was 1066 g ( $\pm 267$  g), 59.5% of the cohort was male, and antenatal steroids were administered to 47 (63.5%) subjects. The Median Clinical Risk Index for Babies II score was 7 (interquartile range 5–10), 6 (8.3%) patients were small for gestational age, 38 (52.0%) received surfactant, and 3 (4.0%) patients died before their seventh day of life.

**Results:** No relationship was found between GIR and IGC during the first 7 days of life (Kruskal-Wallis test,  $p > 0.05$ ).

**Conclusions:** There was no association between GIR and the risk of hyperglycaemia during the first week of life.

## KEY WORDS:

prematurity, hyperglycaemia, continuous glucose monitoring, very low birth weight infants, interstitial glucose concentration.

## INTRODUCTION

Hyperglycaemia in very low birth weight (VLBW) infants is noted frequently, especially during the first days of life. Neonatal hyperglycaemia is defined by absolute thresholds, as well as the length of exposure and degree of glycosuria. Threshold definitions include blood glucose concentrations ranging from  $> 126$  mg/dl to  $> 239$  mg/dl [1], with the most common definition being blood glucose  $> 180$  mg/dl [2]. Because hyperglycaemia

is independently related to increased morbidity and mortality [2–4], many studies have been undertaken to help understand its pathogenesis and aetiology in the VLBW population. Multiple stressful situations, minimal or no enteral feeding tolerance, relative insulin deficiency or resistance, clinical instability, and high glucose infusion rate (GIR) are recognised as risk factors [1–6].

Appropriate parenteral nutrition is a matter of controversy, with the approach to optimal intravenous glucose infusion and its effect on glycaemia changing over time.

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It was previously believed that the glucose supply should be started at a high level. However, it was demonstrated by Chacko *et al.* [7] that gluconeogenesis does not stop in premature infants receiving even high glucose infusions. In previous studies, the association between GIR and hyperglycaemia has been somewhat inconsistent. Indeed, some studies have shown a direct positive relationship, whilst others have not found such a clear correlation [8–11].

Traditional discrete glucose measurements can underestimate the incidence of hyperglycaemia, although more reliable evaluation can be obtained from continuous glucose monitoring systems (CGMs). Continuous glucose monitoring system are validated and safe in the VLBW population, and interstitial glucose concentration (IGC) adequately correlates with blood glucose concentration [12]. However, there are insufficient data concerning the relationship between GIR and glycaemia with the use of CGMs. Obtaining data on this relationship can shed light on the pathophysiology of hyperglycaemia in VLBW infants.

Various methods of glucose control have been proposed as a means of increasing glucose supply in hyperglycaemia, including restricted intake and insulin infusion. However, recommendations for insulin therapy in premature infants are incompatible when considering the risk of causing silent hypoglycaemia or other metabolic changes [2]. In the current study, a standardised nutrition protocol was used as a first-line approach for hyperglycaemia reduction, with adjustments made to the rate of glucose infusion when required. Whether these adjustments to GIR had an impact on glycaemia in VLBW infants was then assessed by use of a CGM system.

The relationship between GIR and IGC in VLBW infants during the first week of life was analysed.

## MATERIAL AND METHODS

### PATIENTS AND INTERSTITIAL GLUCOSE CONCENTRATION

Neonates weighing  $\leq 1500$  g at birth were admitted during their first day of life to the Neonatal Intensive Care Unit of the Department of Paediatrics at Jagiellonian University, in Kraków, Poland. All the recruited patients were hospitalised in this third-level neonatal centre in the period January 2013 – January 2015. Congenital malformations, suspicion of an inborn metabolic disorder, asphyxia perinatal trauma, and a diabetic mother were the exclusion criteria. The Guardian real-time CGM® system (Medtronic, Northridge, CA, USA) was used to measure IGC. The standard IGC range was determined as between 70 and 180 mg/dl. The continuous glucose monitoring sensor application and calibration technique have been previously described [13]. Briefly, measurements were recorded every 5 minutes for 6 days from the CGM sensor inserted into the subcutaneous tissue of the lateral side of the thigh. To calibrate the CGM system, at least 3 times a day, a point-

of-care blood glucose analysis was applied. Fluid, glucose, amino acid, and lipid intakes were assessed at 4-hour intervals during the first week of life. Fluid intakes measured included any volume of fluid given to patients, including nutrition and drugs. The current prospective study was a post hoc analysis of previously collected data.

### GROUPS OF GLYCAEMIA

Based on the median daily value of ICG, patients were divided into 4 groups: Q1 (median IGC below the 25<sup>th</sup> percentile), Q2 (median IGC between the 25<sup>th</sup> and 50<sup>th</sup> percentile), Q3 (median IGC between the 50<sup>th</sup> and 75<sup>th</sup> percentile), and Q4 (median IGC above the 75<sup>th</sup> percentile).

### NUTRITION STRATEGY AND INTERVENTION PROTOCOL

A standardized nutrition protocol for parenteral feeding was provided for all patients, which included minimal enteral nutrition and uniform intervention procedures for hyperglycaemia and hypoglycaemia [14] (see Supplementary Materials). Every modification in nutrient infusion was noted, and the mean daily value for all nutrition components was calculated every 24 hours for each patient.

### ETHICS

Written informed consent was obtained from a parent of each infant.

### STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages, whilst continuous variables are represented by the mean and standard deviation or the median and interquartile range. Differences between groups were compared using the Kruskal-Wallis test, and correlation analysis was performed using Spearman's rank correlation coefficient. Probability values below 0.05 were considered statistically significant. Adjustment for multiple comparisons was done by Bonferroni correction. Statistical analysis was performed using MedCalc software version 20.015 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2021).

## RESULTS

A total of 74 VLBW infants were enrolled into the study. Table 1 presents the characteristics of the study group. The median IGC measurement time was 119.1 hours (range 52.5–164.8 hours) *per* patient. All measurements were obtained in the first week of the patients' lives, starting from the first day. The ranges of median IGC for each group are presented in Table 2. Comparison of glucose intake between the groups is presented in Table 3.

No significant differences were found. Correlation analysis was performed using Spearman's rank correlation coefficient, with no correlation found between glycaemia and glucose intake on any of the 7 days (Figure 1). There was no correlation between protein and lipid intake between groups (data not shown). Median water, lipid, and protein supply are presented in Table 4. A statistically significant difference was found for fluid intake on the third day of observation between the first quartile and fourth quartile groups (Table 5). The number of measurements below 70 mg/dl and 46 mg/dl accounted for 3.56% and 0.29% of all measurements, respectively.

## DISCUSSION

Disturbances in glucose levels are a serious problem among the VLBW population. Its consequences are widely discussed and include increased mortality, as well as morbidities such as sepsis, severe intraventricular haemorrhage, fungal infection, necrotizing enterocolitis, retinopathy of prematurity, poor neurodevelopment, disturbances in growth, and longer hospitalisation [2–4, 6]. Understanding factors that could modify glucose metabolic pathways is important for decreasing

TABLE 1. The characteristics of the study group

| Total group                              | Patients (N = 74)     |
|------------------------------------------|-----------------------|
| Male population, n (%)                   | 44 (59.5)             |
| Median gestational age                   | 28 weeks (IQR 27–31)  |
| Mean birth weight                        | 1066 g ( $\pm$ 267 g) |
| Clinical risk index for babies II score  | 7 (IQR 5–10)          |
| Small for gestational age, n (%)         | 6 (8.3)               |
| Antenatal steroids administration, n (%) | 47 (63.5)             |
| Surfactant administration, n (%)         | 38 (52.0)             |
| Death before seventh day of life, n (%)  | 3 (4.0)               |

IQR – interquartile range

the harmful effects of such disorders. The relationship between hyperglycaemia and intravenous glucose infusion in VLBW infants has been a matter of controversy for a number of years [2, 7, 15]. Here, specific data from the CGM system, alongside precise reports of GIR, has confirmed no association for the first time. Similar results were obtained in the Neonatal Insulin Therapy in the Europe trial, in which the prevalence of hyperglycaemia in the preterm population was investigated. This prospective

TABLE 2. Comparison of daily ranges of median interstitial glucose concentration values between the groups

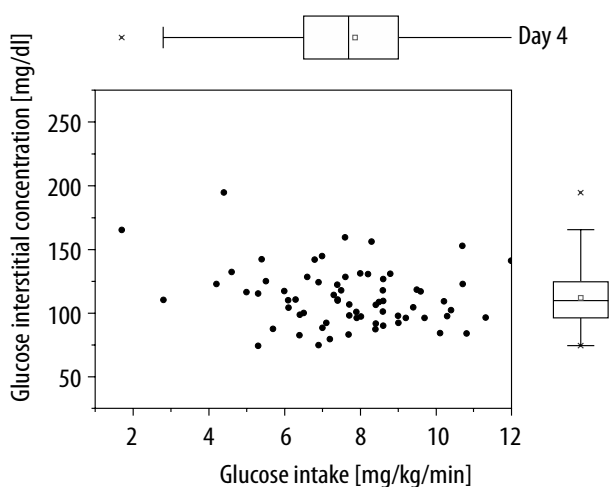
| Parameters | Q1 group |       | Q2 group |        | Q3 group |        | Q4 group |        |
|------------|----------|-------|----------|--------|----------|--------|----------|--------|
|            | Min      | q1    |          | q2     |          | q3     |          | Max    |
| DOL 1      |          |       |          |        |          |        |          |        |
| No.        | 19       |       | 18       |        | 18       |        | 19       |        |
| G          | 72.70    | 99.36 | > q1     | 121.94 | > q2     | 142.71 | > q3     | 213.68 |
| DOL 2      |          |       |          |        |          |        |          |        |
| No.        | 19       |       | 18       |        | 18       |        | 19       |        |
| G          | 71.70    | 92.42 | > q1     | 107.57 | > q2     | 124.92 | > q3     | 222.73 |
| DOL 3      |          |       |          |        |          |        |          |        |
| No.        | 19       |       | 18       |        | 18       |        | 19       |        |
| G          | 70.60    | 94.73 | > q1     | 106.15 | > q2     | 126.16 | > q3     | 185.75 |
| DOL 4      |          |       |          |        |          |        |          |        |
| No.        | 19       |       | 18       |        | 18       |        | 18       |        |
| G          | 74.60    | 96.51 | > q1     | 109.62 | > q2     | 124.37 | > q3     | 194.62 |
| DOL 5      |          |       |          |        |          |        |          |        |
| No.        | 18       |       | 17       |        | 17       |        | 18       |        |
| G          | 63.40    | 92.00 | > q1     | 100.04 | > q2     | 116.62 | > q3     | 186.24 |
| DOL 6      |          |       |          |        |          |        |          |        |
| No.        | 17       |       | 17       |        | 16       |        | 17       |        |
| G          | 60.70    | 87.23 | > q1     | 99.60  | > q2     | 112.49 | > q3     | 164.59 |
| DOL 7      |          |       |          |        |          |        |          |        |
| No.        | 16       |       | 15       |        | 15       |        | 15       |        |
| G          | 71.30    | 91.40 | > q1     | 102.67 | > q2     | 116.70 | > q3     | 187.54 |

DOL – day of life, G – median interstitial glucose concentration (IGC) [mg/dl], No. – number of patients, min – minimal median IGC, q1 – first quartile value, q2 – second quartile value, q3 – third quartile value, max: maximal median IGC

**TABLE 3.** Comparison of glucose intake between the groups based on interstitial glucose concentration

| Day of life | Q1              | Q2              | Q3               | Q4              | Kruskal-Wallis test, <i>p</i> -value |
|-------------|-----------------|-----------------|------------------|-----------------|--------------------------------------|
| 1           | 5.9 (4.53–6.25) | 5.0 (4.58–6.03) | 5.6 (3.45–6.18)  | 5.05 (4.25–6.3) | 0.88                                 |
| 2           | 6.6 (5.1–7.6)   | 6.05 (5.6–6.8)  | 6.3 (5.45–7.0)   | 6.6 (5.2–7.18)  | 0.87                                 |
| 3           | 7.0 (5.86–8.2)  | 7.05 (6.5–7.8)  | 6.35 (5.3–8.2)   | 7.7 (6.78–8.1)  | 0.57                                 |
| 4           | 7.9 (6.98–9.28) | 8.6 (7.75–9.63) | 7.4 (6.01–9.52)  | 7.6 (6.32–8.37) | 0.15                                 |
| 5           | 9.1 (8.4–10.3)  | 8.25(7.3–10.3)  | 9.1 (7.5–10.1)   | 8.2 (6.55–9.4)  | 0.19                                 |
| 6           | 9.5 (8.05–10.9) | 9.2 (7.96–11.2) | 9.05 (8.25–10.6) | 9.3 (7.45–11.2) | 0.99                                 |
| 7           | 9.6 (9.3–10.95) | 9.3 (7.9–11.43) | 9.35 (8.5–10.0)  | 9.3 (7.0–11.8)  | 0.72                                 |

Q1–Q4 – quartile groupings of glycaemia

Glucose intake is shown as: median (1<sup>st</sup>–3<sup>rd</sup> quartile) [mg/kg/min].**FIGURE 1.** Correlation between glycaemia and glucose intake for day 4

analysis of CGM data indicated a lack of association between the rate of dextrose infusion and hyperglycaemia [8]. Fernández-Martínez *et al.* presented data comparing CGM with traditional monitoring [10]. Furthermore, Tottman *et al.* indicated that carbohydrate intake was not independently associated with hyperglycaemia, although after correction for gestational age and birth weight, the odds of hyperglycaemia increased with GIR [9]. In contrast, Zamir *et al.* demonstrated that glucose infusion had only a minimal impact on glucose concentrations in VLBW infants during the Extremely Preterm Infants in Sweden Study [15]. Also, Stensvold *et al.* showed that an intermediate GIR (5.1–7.0 mg/kg/min) and high GIR (above 7.0 mg/kg/min) were significant independent predictors of severe hyperglycaemia compared to a low GIR (below 5.1 mg/kg/min) [11].

**TABLE 4.** Mean daily fluids, lipids, and protein supplied

| DOL                    | 1           | 2           | 3            | 4            | 5            | 6            | 7            |
|------------------------|-------------|-------------|--------------|--------------|--------------|--------------|--------------|
| Fluids supply [ml/kg]  | 79.5 (20.6) | 91.9 (15.2) | 101.5 (19.1) | 113.3 (22.5) | 120.8 (25.2) | 124.8 (25.2) | 125.0 (23.6) |
| Lipids supply [g/kg]   | 1.3 (0.6)   | 1.8 (0.6)   | 2.4 (0.6)    | 3.0 (0.6)    | 3.4 (0.6)    | 3.7 (0.6)    | 3.8 (0.7)    |
| Proteins supply [g/kg] | 1.8 (0.7)   | 2.3 (0.5)   | 2.7 (0.5)    | 3.1 (0.6)    | 3.4 (0.5)    | 3.5 (0.6)    | 3.7 (1.2)    |

Data are presented as mean and standard deviation.

**TABLE 5.** Comparison of fluid intake between the groups

| Day of life | Q1                 | Q2                  | Q3                  | Q4                  | Kruskal-Wallis test, <i>p</i> -value |
|-------------|--------------------|---------------------|---------------------|---------------------|--------------------------------------|
| 1           | 79.5 (36.8–165.0)  | 80.0 (52.2–100.7)   | 80.0 (30.7–106.1)   | 90.5 (30.4–110.3)   | 0.3                                  |
| 2           | 91.0 (74.1–114.2)  | 83.3 (75.5–103.0)   | 87.7 (80.6–139.0)   | 97.0 (75.5–140.4)   | 0.06                                 |
| 3           | 93.0 (65.7–118.8)  | 92.8 (68.4–146.5)   | 98.5 (77.8–145.0)   | 103.3 (89.3–151.9)  | 0.016                                |
| 4           | 105.4 (68.6–131.7) | 108.7 (89.9–165.3)  | 108.3 (82.8–171.0)  | 119.0 (87.4–182.7)  | 0.17                                 |
| 5           | 115.8 (93.5–179.8) | 112.5 (83.0–145.3)  | 114.3 (91.8–142.8)  | 132.3 (77.8–181.6)  | 0.09                                 |
| 6           | 117.7 (64.6–156.4) | 118.75 (52.6–148.1) | 119.4 (88.3–182.3)  | 129.1 (106.7–201.2) | 0.07                                 |
| 7           | 113.8 (97.6–149.1) | 121.6 (82.0–183.5)  | 112.9 (102.0–160.0) | 131.8 (101.2–215.6) | 0.1                                  |

Q1–Q4 – quartile groups of glycaemia

In all the studies mentioned above, discrete glucose measurements were taken *via* a CGM system. Differences in results found in these studies may arise from the influence of other nutritional elements such as amino acids, and other modifications to the glucose infusion. Tottman *et al.* showed that decreased fat and carbohydrate intake, as well as increased protein intake, were associated with a decrease in the incidence of neonatal hyperglycaemia, with no impact on hypoglycaemia [9]. This association may be partially explained by the potentiation of insulin secretion by individual amino acids such as arginine, leucine, and glutamine [16, 17]. Furthermore, Tottman *et al.* started with 2.3 g/kg/day of protein intake compared with 2 g/kg/day in the Fernández-Martínez *et al.* trial, and 1 g/kg/day in the trial by Burgess *et al.* [9, 10, 16]. In our study, no relationship was found between protein or lipid intake, which was provided in similar quantities to previous trials, and IGC.

Significant differences in fluid intake between groups was probably the consequence of glycaemia regulation, based on the nutritional strategy used; nevertheless, this requires further investigation. Previous analysis showed no correlation between intravenous fluid intake and glycosuria, which does not strongly support the idea that increased fluid intake was a response to polyuria in this case [13]. Additionally, premature infants do not stop endogenous glucose production when receiving parenteral nutrition corresponding to their normal glucose production rate, which is 6–8 mg/kg *per* minute [18]. Chacko *et al.* showed that gluconeogenesis was not deactivated even if premature infants received intravenous glucose at rates exceeding their normal glucose production rate (as a part of total parenteral nutrition consisting of glucose, lipids, and amino acids) [7]. Even if the intravenous glucose supply was reduced to half their normal glucose production rate (approximately 3 mg/kg *per* min), glucose produced *via* gluconeogenesis was enough to maintain normoglycaemia for periods of at least 10–12 hours [7, 19]. Also, immaturity of glucose transporters in the liver may be a cause of this phenomenon [20]. Together, these studies indicate that gluconeogenesis is independent of glycaemia and glucose intake in preterm infants. The glucose infusion rate needed to maintain normoglycaemia is lowest in the first day of life and increases up to the seventh day. Perri *et al.* and Galderisi *et al.*, who started with a similar GIR to our study, demonstrated that glucose varied between patients and increased day by day [21, 22].

Glucose derived from gluconeogenesis may be insufficient or be at the expense of other metabolic pathways. On the other hand, glucose uptake to cells forced by insulin can have negative consequences such as overwhelming mitochondrial oxidative capacity, increasing reactive oxygen species production, and promotion of fatty acid production [23]. Importantly, severe metabolic acidosis or ketonuria were not observed in this study. Evidence from animal studies suggests that neonatal hypoglycaemia appears to be a hypoketotic state,

with variable levels of lactate [24]. During this early time frame lactate may be a more important alternative energy source than ketones. Whether or not the maintenance of normoglycaemia driven by low glucose supply, independent of glucose transport to dedicated cells forced by insulin, leads to an energy deficit at this level requires further investigation.

Reducing the intravenous glucose supply, as long as the blood (or interstitial) glucose level is normal, seems to be rational and safe. However, it is only possible when CGM systems are used in clinical practice. Such monitoring systems have found their place in clinics in recent years, meaning that controlling glycaemia by modifying intravenous glucose infusion should be easy to achieve. Our recent studies have demonstrated the effectiveness of CGM systems in early prevention of both hyperglycaemia and glycaemic variability, which has minimised the harmful effects of glucose on VLBW infants [13, 14, 25].

Limitations of this study include the small number of patients and the fact that none of the patients were treated with insulin. Additionally, investigating the relationship between intravenous glucose intake and hyperglycaemia was not the primary aim of the study.

## CONCLUSIONS

There was no association between IGC and GIR. This study strongly supports the idea that the nutritional strategy for VLBW preterm infants should be guided by glucose concentration rather than GIR, with the use of the CGM system. The use of GIR in most cases leads to normal or only slightly elevated glucose levels. However, in selected cases, clinically significant hyperglycaemia may be the result of additional variables related to the patient's health condition.

## DISCLOSURES

1. The study was part of a project supported by grant no RG3/2012/3 “Early glycemic profile and the risk of complications of prematurity” obtained from the Nutricia Foundation.
2. The study protocol was approved by the Jagiellonian University Bioethics Committee.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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