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Clinically stable very low birthweight infants are at risk for recurrent tissue glucose fluctuations even after fully established enteral nutrition

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ABSTRACT

Objective In previous cases, we have observed occasional hypoglycaemic episodes in preterm infants after initial intensive care. In this prospective study, we determined the frequency and severity of abnormal tissue glucose (TG) in clinically stable preterm infants on full enteral nutrition.

Methods Preterm infants born at <1000 g (n=23; G1) and birth weight 1000–1500 g (n=18; G2) were studied at a postmenstrual age of 32±2 weeks (G1) and 33 ±2 weeks (G2). Infants were fed two or three hourly, according to a standard bolus-nutrition protocol, and continuous subcutaneous glucose measurements were performed for 72 h. Normal glucose values were assumed at ≥2.5 mmol/L (45 mg/dL) and ≤8.3 mmol/L (150 mg/dL). Frequency, severity and duration of glucose values beyond normal values were determined.

Results We observed asymptomatic low TG values in 39% of infants in G1 and in 44% in G2. High TG values were detected in 83% in G1 and 61% in G2. Infants in G1 experienced prolonged and more severe low TG episodes, and also more frequent and severe high TG episodes. In G1 and G2, 87% and 67% of the infants, respectively, showed glucose fluctuations characterised by rapid glucose increase followed by a rapid glucose drop after feeds. In more mature infants, glucose fluctuations were less pronounced and less dependent on enteral feeds.

Conclusions Clinically stable well-developing preterm infants beyond their initial period of intensive care show interstitial glucose instabilities exceeding values as low as 2.5 mmol/L and as high as 8.3 mmol/L. This novel observation may play an important role for the susceptibility of these high-risk infants for the development of the metabolic syndrome.

Trial registration number German trial registration number DRKS00004590.

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What is already known on this topic

▶ Preterm infants are at risk for postnatal metabolic instability.
▶ Instabilities occur during immediate postnatal intensive care while on parenteral nutrition.
▶ Both high and low glucose levels are associated with poor outcome.

What this study adds

▶ This is the first prospective study showing that metabolic instabilities still occur in very low birthweight infants at a median-corrected gestational age of 32 4/7 or 37 days of life.
▶ Metabolic instability remains, especially in extremely low gestational age infants while already clinically stable and already on full enteral nutrition.
▶ Continuous tissue glucose monitoring is able to identify infants at risk for metabolic instabilities at a median-corrected gestational age of 32 4/7 or 37 days of life.

67% of infants who were SGA during their first 6 h of life. Alexandrou et al[2] diagnosed hypoglycaemia (<2.6 mmol/L) in 41% and hyperglycaemia (>8.3 mmol/L) in 81% of preterm infants during the first week of life and reported an association of hyperglycaemia with death and white matter reduction. Lucas et al[3] described hypoglycaemic events (<2.6 mmol/L) in 39% of infants with birth weight <1000 g in the first month, which in 10% were still detected after the fourth week of life.

Previous studies were based on repeated capillary, arterial or venous glucose measurements, and usually glucose measurements are frequently performed during the first days of life, successively reduced and, therefore, only rarely performed once the infants have reached full enteral nutrition.

In a previous chart analyses, we detected occasional hypoglycaemic episodes in clinically stable formerly preterm infants fed on a standard bolus-feed protocol with both enriched breast milk as well as preterm formula.[4] Based on these observations, we hypothesised that clinically stable very low birthweight (VLBW) preterm infants are still

INTRODUCTION

Hypoglycaemic and hyperglycaemic events in the first hours, days and weeks of life are associated with risk factors, such as low gestational age (LGA), low birth weight, being born small for gestational age (SGA), and maternal conditions, like pregestational or gestational diabetes among other conditions both in the neonate and the mother.

Various authors described an incidence of hypoglycaemia and hyperglycaemia at different postnatal ages. Lubchenco and Bard[1] reported hypoglycaemia (<1.7 mmol/L) in 15% of preterm infants who were appropriate for gestational age and in

susceptible to developing asymptomatic fluctuations of glucose levels once on full enteral nutrition. In this prospective study, we aimed to determine the frequency and severity of tissue glucose (TG) fluctuations in VLBW infants after having reached full enteral feeds over a 72 h period using a continuous glucose monitoring system (CGMS).

PATIENTS AND METHODS

We conducted a prospective observational cohort study (German trial registration number DRKS00004590) with continuous subcutaneous glucose monitoring of preterm infants at the Division of Neonatology, Perinatal Center, LM-University Munich, Germany, Campus Grosshadern, and at the Neonatology Department of the Regional Hospital in Bolzano, Italy. The institutional ethical committees in both hospitals approved the study, and parental informed consent was obtained prior to enrolment. Patients were recruited between April 2011 and February 2013 in both centres. Inclusion criteria were (1) birth weight <1500 g, (2) gestational age <32 weeks postmenstrual age, (3) on full enteral feeds for at least 5 days and (4) otherwise clinically stable (no invasive respiratory support, no signs of infection, no severe desaturation—SpO_2 <80%—and bradycardia heart rate <80/min). Exclusion criteria were (1) a pathological neonatal metabolic screening test on the third day of life (DOL) (routine testing in newborns to screen for certain genetic, metabolic and endocrine disorders), (2) a positive family history for metabolic diseases, (3) major congenital malformations and (4) any acute illness requiring intensive care intervention.

Infants were stratified into two groups according to birth weight: <1000 g (G1, n=23) and 1000 g—1500 g (G2, n=18), as we have previously observed occasional low blood glucose values in formerly preterm infants especially in infants born at <1000 g.[4] Infants at extremes of their gestational age-related birth weight (SGA, LGA) are at increased risk for glucose instabilities.[1] [5–7] Thus, we decided to stratify infants by birth weight rather than gestational age at birth.

Subcutaneous TG was measured continuously over 72 h with a standard CGMS (CGMS; Guardian REAL-time, Soft sensor, Medtronic GmbH, Meerbusch, Germany). The sensor tip was manually inserted under sterile conditions through the intact skin in the subcutaneous tissue of the infant's thigh. It has a platinum electrode that catalyses interstitial glucose oxidation

and determines average values every 5 min. Results are transferred wirelessly to a receiver displaying them in real time.

Intermittently, capillary blood samples were analysed with a 'point of care' (POC) blood gas analyser (Amperometric glucose measurement, Radiometer, ABL 700, Copenhagen, Denmark), to calibrate the subcutaneous sensor. The POC device is regularly quality insurance tested for three ranges of values: (1) glucose values <2.5 mmol/L (median 1.6 mmol/L, CI 1.44 to 1.66 mmol/L), (2) glucose values <6.6 mmol/L (median 5.7 mmol/L, CI 5.40 to 5.58 mmol/L), (3) glucose values >13.9 mmol/L (median 14.2 mmol/L, CI 12.13 to 14.95 mmol/L).

These blood glucose readings were compared with the values obtained by the CGMS in order to assess the accuracy of the device. In order to evaluate the accuracy of the CGMS method, we calculated the correlation between paired glucose readings from capillary blood samples measured with a POC blood gas analyser and the corresponding CGMS interstitial glucose values (R^2=0.57, p<0.001; n=307; Pearson's correlation coefficient; Wilcoxon Signed Rank test). On Bland–Altman analysis, the mean difference between both monitoring systems was −0.011 mmol/L (95% CI −0.13 to 0.11, IQR 4.5–6.1 mmol/L; figure 1). The use of the CGMS has previously been validated to detect periods of hyperglycaemia and hypoglycaemia in preterm infants and in term infants at risk of glucose fluctuations.[8–10] Unfortunately, normal values of CGM in the neonatal period of healthy term infants are not available. During the whole study, we did not detect any adverse effect of CGM in preterm infants, especially, no local or systemic infection associated with the application of the sensor was observed.

All infants were fed according to a standard bolus-feeding protocol where full enteral nutrition was provided at 150–180 mL/kg/day with fortified breast milk or preterm formula at 110–135 kcal/kg/day two, three or four hourly depending on the age, and the tolerance of the intakes. The feeding protocol was according to the recommendations of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition for preterm infants.[11]

Despite the fact that the plasma glucose concentrations that define low and high glucose values in newborns are without rigorous scientific justification,[12–15] [16] we adopted thresholds for low TG values (≤2.5 mmol/L; ≤45 mg/dL) and high TG values by two cut-off levels, (>8.3 mmol/L; >150 mg/dL and

Figure 1 Bland–Altman Plot, continuous glucose monitoring system (CGMS) versus point of care (ABL). Horizontal axis represents the mean of the sensor (CGMS) and point-of-care glucose measurement (mmol/L). Vertical axis represents the difference between the sensor (CGMS) and the point-of-care glucose measure (mmol/L). Solid lines indicate ±2SD.
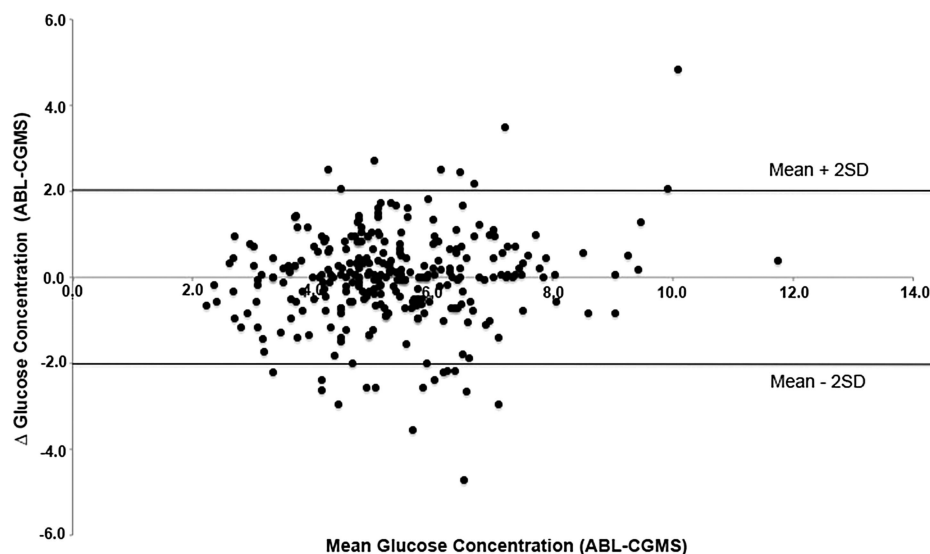
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>11.1 mmol/L; >200 mg/dL) in accordance with previous studies on blood glucose.[2 17–19]

The variability of TG was calculated as the SD of TG values per infant throughout the study period (TG-SD).[20 21] In order to identify possible risk factors associated with high-amplitude TG fluctuations, we correlated individual SD values with potential risk factors for glucose instability: gestational age at birth and at trial entry, nutritional components like total fluids, carbohydrates, protein and lipids, as well as total days on parenteral nutrition prior to CGM. Additionally, the Clinical Risk Index for Babies (CRIB-Score) and the Body Mass Index (BMI) at birth were calculated and evaluated. The CRIB score is a composite score for preterm infants born at <1500 g, derived from birth weight, gestational age, lowest base excess, minimal and maximal FiO2 within the first 12 h of life and malformations. Thus, a high CRIB-score is an indicator for poor outcome.[22]

Data were analysed using the Statistical Package for Social Sciences V.20.0 (SPSS, Chicago, Illinois, USA).

Statistical analysis within cohorts was carried out with χ^2 tests to rule out any effect of confounding factors. For the calculation of significance levels across cohorts, non-parametric Mann–Whitney U test or a Kruskal Wallis test was used. Since many of the variables were not distributed normally, the median and IQRs for both cohorts were calculated and are the main measures reported. Risk factors were correlated to TG-SD by Pearson's correlation. Further analysis of these factors was achieved by stepwise linear regression analysis. The level of significance was set at p<0.05.

RESULTS

Table 1 displays demographics and characteristics of infants enrolled in both strata at birth and at trial entry. The infants in both groups were enrolled at a median-corrected postmenstrual age of 37 DOL (IQR: 31 DOL–48 DOL) and a median-corrected gestational age of 33 weeks (IQR: 31 3/7–34 3/7).

TG values obtained with the CGMS showed cyclic fluctuations exceeding 2.5 mmol/L and 8.3 mmol/L throughout the day. Typically, high TG peaks were followed by rapid drops concomitant with the feeding schedule. These fluctuations occurred regardless of whether the infant was fed two, three or four hourly. By contrast, TG fluctuations were less pronounced and remained within the predefined range in G2, despite the fact that both groups were approximately 33 weeks corrected postmenstrual age at trial entry (median—IQR: 31 3/7–34 3/7). The majority of infants (75%) were fed three hourly. In figure 2, the combined measurements of all these infants is outlined as mean ±2SDs, with the grey area indicating the presumed normal range of 2.5–8.3 mmol/L (figure 2).

TG values fluctuated beyond the predefined limits in 20/23 (87%) infants in G1 and 12/18 (67%) infants in G2. Only nine of the 41 enrolled infants (22%, 3/23 in G1 and 6/18 in G2) had stable TG values within the normal range throughout the entire study period (table 2).

Of all infants, 12% showed at least one episode of low TG, 37% had at least one episode of high TG and 29% suffered both low and high TG throughout the monitored time. The occurrence of low TG was similar in both groups (39% in G1 and 44% in G2), whereas high TG was more frequent in G1 (83%) compared with G2 (61%, table 2).

In G1, 1/23 (4%) infants had very low TG (<1.7 mmol/L/ 31 mg/dL) and 8/23 (35%) values between 1.7 and 2.5 mmol/L (31–45 mg/dL). In G2, 8/18 (44%) presented TG values <2.5 mmol/L (<45 mg/dL), whereas no infant developed values below 1.7 mmol/L (31 mg/dL). Considering the high TG threshold >8.3 mmol/L (150 mg/dL), 8/23 (35%) in G1 and 9/18 (50%) in G2 developed recurrent high TG episodes. A TG value above 11.1 mmol/L (200 mg/dL) was observed in 11/23 (48%) infants in G1 and 2/18 (11%) in G2 (table 2 and figure 3A–C). Figure 3C illustrates the duration and severity of all 402 recorded low and high TG episodes.

Of the registered 38 episodes of low TG values among all infants, 12/38 (32%) lasted <10 min, 12/38 (32%) lasted 10–30 min, 9/38 (24%) lasted 30–60 min and 5/38 (13%) lasted >60 min. Seventeen patients had hypoglycaemic episodes during the 72 h monitoring. Of these 17 patients, 10 (59%) had only one hypoglycaemic episode and seven (41%) had more than one hypoglycaemic episodes. Of the infants with recurrent hypoglycaemic episodes, four were in G1 and three belonged in G2.

Table 1 Infants' characteristics (median—IQRs)

	BW <1000 g	BW 1000–1500 g
Baseline		
Number	23	18
Gestational age (weeks)	25 5/7 (24 1/7–27)	29 6/7 (28 5/7–30 3/7)
Birth weight (g)	672.5 (615–900)	1210.0 (1152.5–1327.5)
BMI	6.8 (6.3–7.3)	7.7 (7.1–8.4)
SGA (%)	17	11
Male (%)	65	72
Antenatal glucocorticoids (%)	91	100
Caesarean section (%)	87	89
CRIB score	7 (2–8)	1 (1–1.25)
At study entry		
Day of life	47.0 (38–53)	31.0 (26–36)
Gestational age (weeks)	32 2/7 (30 4/7–33 5/7)	33 5/7 (32 5/7–34 6/7)
Weight (g)	1350.0 (1246.25–1510)	1650.0 (1570–1805)
Length (cm)	39.0 (36.0–41.0)	41.8 (41–42.6)
Head circumference (cm)	27.0 (25.5–29.0)	28.8 (28.0–29.9)
Total length of parenteral nutrition (days)	17 (12–23)	12 (9–13)
Days after end of total parenteral nutrition	28 (18–43)	19 (15–23)

BMI, Body Mass Index; CRIB, Clinical Risk Index for Babies; SGA, small for gestational age; BW, birth weight.

Figure 2 Cumulated tissue glucose (TG) tracings from all infants on 3-hourly bolus feeds (eight feedings per day, n=31). Black line indicates mean tissue glucose within 24 h; grey lines indicate 2SD TG values indicating meal-associated fluctuations. Grey area outlines the normal range >2.5 mmol/L–≤8.3 mmol/L.
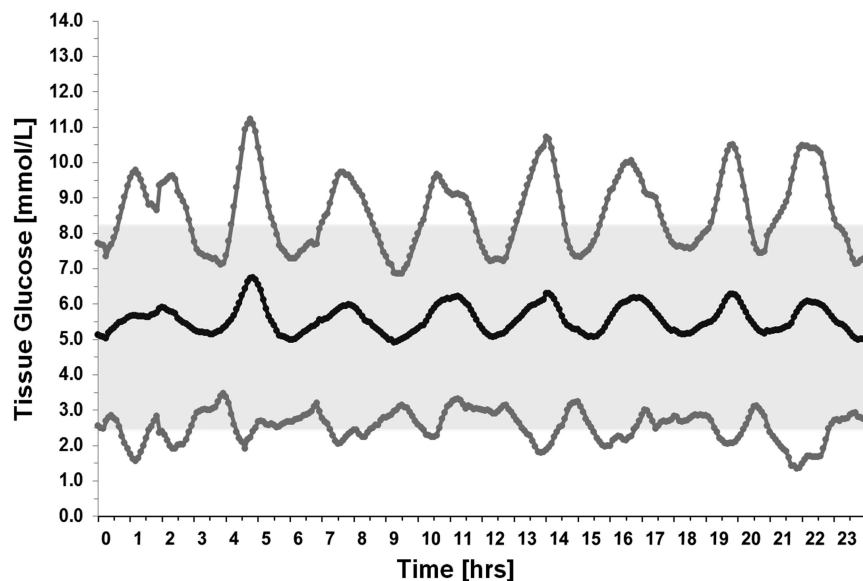
A total of 305 episodes with high glucose values between 8.3 and 11.1 mmol/L were recorded. Of those, 13 (4%) lasted <10 min, 174 (57%) lasted 10–30 min, 67 (22%) lasted 30–60 min and 51 (17%) lasted >60 min. Of the 59 episodes of severe high TG episodes (>11.1 mmol/L), 2 (3%) lasted <10 min, 32 (54%) between 10 min and 30 min, 12 (38%) lasted 30–60 min and 13 (22%) lasted >60 min (figure 3D).

TG-SDs were negatively correlated with the gestational age at birth (R=−0.43; 95% CI −0.64 to −0.06), the gestational age at study entry (R=−0.42; 95% CI −0.64 to −0.15), the BMI at birth (R=−0.32; 95% CI −0.53 to −0.06), and positively correlated with the total days on parenteral nutrition (R=0.56; 95% CI 0.21 to 0.74), as well as the CRIB-score at birth (R=0.43; 95% CI 0.11 to 0.61). In the linear regression model, only the number of days on total parenteral nutrition remained a significant risk factor for TG fluctuations (p=0.02) and the gestational age at study entry just missed significance (p=0.07). Nutritional components, total fluids and BMI at birth had no effect on TG-SD. TG variability was not related to gender, mode of delivery, bronchopulmonary dysplasia, IVH (intraventricular haemorrhage) and periventricular leukomalacia. We could not detect any significant difference in weight gain 7 days before and after the monitoring period, either among cohorts or when trying to relate them to low or high glucose events. However, the nine infants in this study (3/23 in G1 and 6/18 in G2) with glucose

values within the predefined glucose range of 2.5–8.3 mmol/L showed a significantly better weight gain than unstable ones (p=0.046).

DISCUSSION

In this study, we report for the first time glucose instabilities in preterm infants after their initial postnatal period of intensive care. The infants in our study were clinically stable on full enteral bolus nutrition without any potential reason for glucose fluctuations beyond normal limits. In general, clinically stable preterm infants are assumed to be also metabolically stable as soon as blood glucose measurements have repeatedly returned values within a normal range. As a result, further blood glucose measurements are normally not routinely performed.[18] [23] To date, we are not able to conclude whether our novel findings on TG are worrisome, because there are no normal TG values available for preterm infants. However, several authors reported that repeated episodes of hypoglycaemia with values <2.6 mmol/L in the early postnatal period, both symptomatic and asymptomatic, impair neurodevelopment.[3] [24–26] Hypoglycaemia is associated with reduced brain growth and neonatal brain injury.[24] [27–29] Additionally, hyperglycaemia in the first week of life has been described as a risk factor associated with death, severe IVH and white matter reduction.[2] [19]

Alexandrou et al[2] reported that only 10 of 113 infants born at <27 weeks gestational age maintained a normoglycemic level in the first week of life. We performed glucose measurements between the third and eighth week of life and registered 38 episodes of low glucose episodes, 305 of moderately high glucose episodes (>8.3 mmol/L–150 mg/dL) and 59 events of severely elevated levels with TG levels >11.3 mmol/L/200 mg/dL. After the first 10 DOL, frequent glucose measurements are not considered to be needed in clinically stable infants without risk factors, especially after reaching full enteral feeds.[12] [30] The high incidence of high and low glucose levels detected in this study by CGMS demonstrates for the first time that this assumption does not hold true for former VLBW infants. These prospective data confirm our previous retrospective chart analysis.[4] For VLBW infants, the difficulty to maintain their systemic glucose level within a normal range seems to continue even after the first month of life, despite clinical stability and full enteral nutrition according to current nutritional guidelines.[11]

Table 2 Results

|	BW <1000 g	BW 1000–1500 g
Number	23	18
Infants with tissue glucose fluctuations	87% (20)	67% (12)
Stable infants	13% (3)	33% (6)
Incidence of low tissue glucose values	39%	44%
Tissue glucose values <1.7 mmol/L	4% (1)	–
Tissue glucose values 1.7–2.5 mmol/L	35% (8)	44% (8)
Incidence of high tissue glucose values	83%	61%
Tissue glucose values >8.3 mmol/L	35% (8)	50% (9)
Tissue glucose values >11.1 mmol/L	48% (11)	11% (2)

BW, birth weight.

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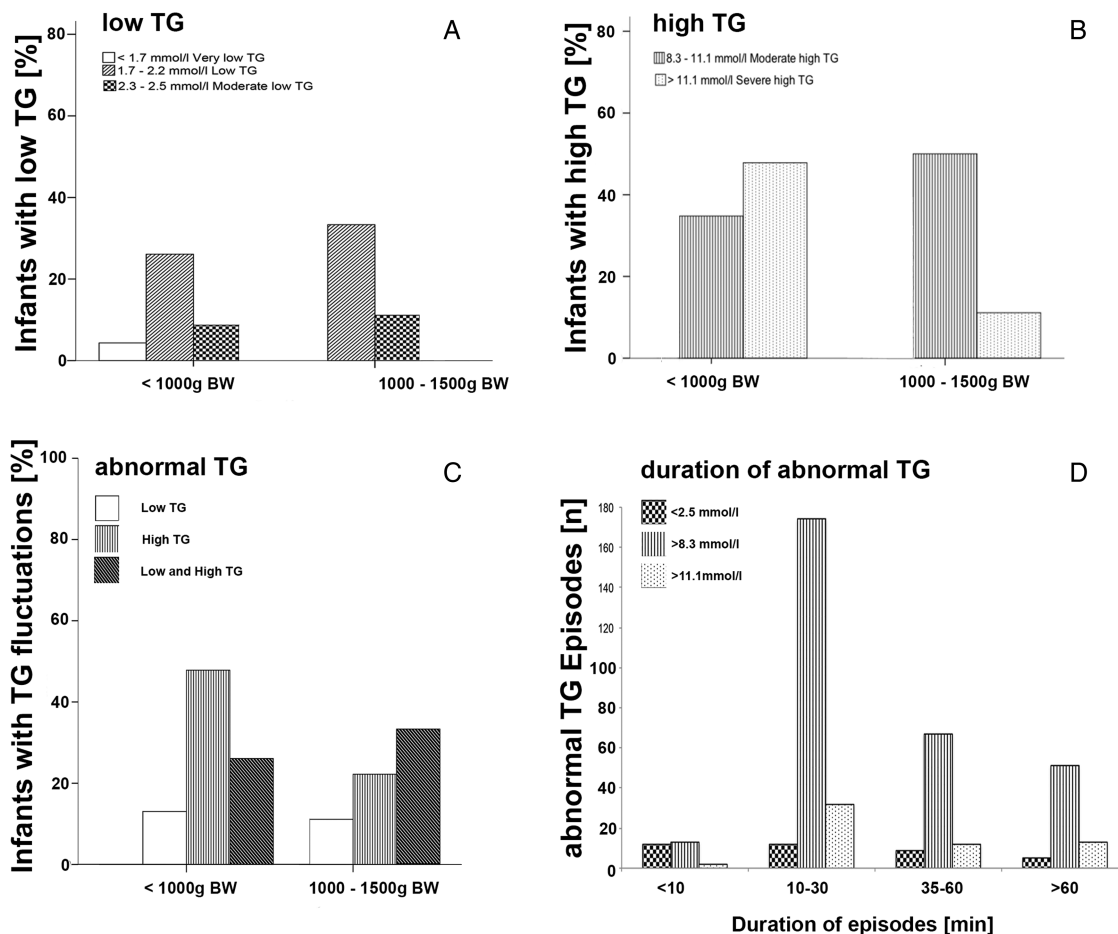
Figure 3 (A–D) Frequency (% of infants in cohort) of low (A) and high (B) tissue glucose (TG) episodes with regard to severity in both weight cohorts. (C) Overall frequency (% of infants in cohort) of abnormal TG. (D) Duration and severity of all recorded episodes.

All the 402 registered low and high glucose episodes in this study were asymptomatic. This finding is of major concern, as both extremes have been demonstrated previously to potentially harm these infants.[3 21 22 24 25 27]

By using CGMS, we were able to assess the duration of glucose values beyond the normal range. Almost one quarter of the low glucose episodes lasted between 30 and 60 min, whereas the more frequent high glucose episodes lasted usually between 10 and 30 min, and in 17% >60 min. It is quite worrying that VLBW infants show high glucose levels at this age, since the same glucose values in the first week of life are associated with increased mortality and white matter reduction.[2] Additionally, we registered episodes of high TG, of which 54% lasted 10–30 min, 20% between 30 and 60 min and 22% longer than 60 min. Several follow-up studies have shown that previously preterm infants are at risk for intima thickening of vessels and for the development of metabolic syndrome later in life.[31–33] Our data might provide the link between these findings and the cause of future sequelae of extremely preterm infants as we find especially high prevalence of high TG in these infants.

A weakness of our study is the low sample size. Nevertheless, the variability of TG (TG-SD) in our two cohorts decreases with increased gestational age at birth, a higher BMI at birth as well as with increased postmenstrual age at the time of measurements. And the duration of parenteral nutrition, typically shorter in more mature infants, remained significant in the linear regression model.

Despite not reaching significance in the regression model, all our data point to prematurity per se being the major risk factor

for glucose instabilities after birth. It has been shown in the past that metabolic adaptation in preterm infants differs from infants born at term. Immature neonates (24–29 weeks gestational age and birth weight between 600 and 1200 g) can produce glucose via glycogenolysis and gluconeogenesis at rates comparable with term newborns during their first DOL, but the functional immaturity of the enzymatic systems increases the propensity to hypoglycaemic episodes.[18 34 35] During the first postnatal week, the relation between glucose and other energy sources in preterm infants are low because they cannot sustain gluconeogenesis at the same rate as term newborns. The accumulation of glycogen, fat and protein occurs only in the last 8 weeks of pregnancy, and since VLBW infants are born substantially earlier, they are not able to tolerate long periods of fasting.[18 34] Blood glucose values have been shown to vary more in preterm infants after birth. On one hand, the immaturity of the glucose sensor in the pancreatic β cell leads to an inability to downregulate insulin secretion during hypoglycaemia. On the other hand, the hepatocyte response to the circulating insulin concentrations during hyperglycaemia is immature as well, instead continuing with their glucose production.[17]

The relative lack of adipose tissue (<2% of total body weight) and glycogen stores in this group of neonates results in an incapability of producing alternative fuels to maintain euglycaemia via glycogenolysis and gluconeogenesis for long periods of fast, causing a limitation for protective metabolic counterregulation during hypoglycaemia.[18] In preterm infants, the endocrine and enzyme control of intermediate metabolism is

immature and not fully developed, leading to a failed homeostasis. They are less able than term infants to adapt to cessation of intrauterine nutrition, and they depend partly on total parental nutrition during the first weeks of life.[17 34 36 37]

Preterm infants also have lower ketone body concentrations, even at lower glucose values, than term infants.[36] Glucose-regulated insulin secretion (first detected at the 11th week of gestation, but not released until the 20th week) by the pancreatic β cell is still immature in preterm infants, resulting in unregulated and inadequate insulin production and secretion. The plasma insulin concentration and the insulin/glucose ratio increase exponentially with gestation, indicating the maturation of the pancreas.[18 35] In our study, insulin secretion was not determined due to ethical reasons. TG values determined by CGM measurements very well represent blood glucose values even in preterm infants.[38] However, TG values change mirror glucose values with a substantial time delay of about 20 min. Thus, repeated blood samples would have been necessary to actually determine corresponding blood insulin levels. However, we speculate that immature glucose metabolism at the time of our measurements is responsible for glucose derailments detected in this study. The preterm organism is, most likely, not yet equipped to deal with repeated high caloric bolus nutrition, a usual practice in neonatal intensive care units today.[18 23 36 37] Current feeding practices for preterm neonates involve small bolus meals, for example, every 2–4 h.

CONCLUSION

The incidence of low and high glucose episodes without any clinical signs in stable, fully enteral-fed preterm infants is high. This is the first study to describe glucose instability in these infants, and prematurity may be a key factor for this phenomenon. Whether breast milk fortification is responsible and whether persisting glucose fluctuations in preterm infants have a long-term effect with regard to somatic and neurological development in these infants require further studies.

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Clinically stable very low birthweight infants are at risk for recurrent tissue glucose fluctuations even after fully established enteral nutrition

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Notes