Relationship between Measures of Neonatal Glycemia, Neonatal Illness, and 2-Year Outcomes in Very Preterm Infants

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Objectives To investigate relationships between early neonatal glycemia, neonatal characteristics, neonatal illness, and developmental outcomes in very preterm infants.

Study design A retrospective, observational cohort study of 443 infants born weighing <1500 g or <30 weeks of gestation, and admitted within 24 hours to National Women's Hospital, Auckland, New Zealand. Glucose variability was defined as the standard deviation around the mean after log transformation of all blood glucose concentrations. Absolute glycemic excursions in the first week were used to divide the infants into 4 groups: normoglycemic; hypoglycemic; hyperglycemic, and unstable.

Results Compared with normoglycemic infants, hypoglycemic and unstable infants had lower birth weight *z*-scores, and hyperglycemic and unstable infants were of lower birth weight. Hypoglycemic infants had similar outcomes to normoglycemic infants. Hyperglycemic and unstable infants were less likely to survive without neonatal morbidity and less likely to survive without neurodevelopmental impairment at 2 years of age. Higher mean blood glucose concentration was seen in the hyperglycemic and unstable groups, and was associated with worse neonatal and 2-year outcomes. Greater glucose variability was seen in the hypoglycemic and unstable groups, and was associated with worse neonatal illness but not outcome at 2 years. No associations between measures of neonatal glycemia and neonatal or 2-year outcomes remained after correction for gestation, birth weight *z*-score, and socioeconomic status.

Conclusions In very preterm infants, measures of neonatal glycemia are markers of gestational age and intrauterine growth, and are not independent predictors of neonatal illness or outcomes at 2 years of age. *(J Pediatr 2017;188:115-21).*

Infants born very preterm and at very low birth weights are at risk of adverse neurodevelopmental and health outcomes.[1,2] Some of these outcomes have been linked to the metabolic vulnerability that is associated with preterm birth. Specifically, preterm infants are at risk of both hypoglycemia and hyperglycemia.[3-5] Neonatal hypoglycemia has been associated with brain injury,[6] visual impairment,[7] and impaired cognitive performance in childhood.[8] In very preterm infants, hyperglycemia has been associated with increased rates of sepsis,[9] retinopathy of prematurity,[10] intraventricular hemorrhage,[11] and abnormal neurologic examination at 2 years of age.[12] Neonates with hyperglycemia commonly are treated with insulin,[13] which substantially increases their risk of hypoglycemia[14,15] and is likely to increase glucose variability.[12]

In critically ill adults and children, high glucose variability is itself associated with increased morbidity and mortality.[16-19] However, it is not clear if this relationship is causal or if increasing glucose variability merely signals deteriorating homeostatic function secondary to illness. Relationships between glucose variability and mortality have been observed in very low birth weight infants,[5] term neonates, and children undergoing intensive care.[20,21] It is not known if these relationships can be explained by the associated degree of absolute hypoglycemia or hyperglycemia, or whether glucose variability alone relates to outcomes, even in normoglycemic neonates.

The purpose of this study was to characterize very preterm infants with different glucose profiles in the first week after birth, and to investigate the relationships between neonatal glucose profiles (absolute glycemia, mean blood glucose concentration, and glucose variability), neonatal illness, and developmental outcomes at 2 years of age.

Methods

Eligible infants were born weighing <1500 g or at <30 weeks of gestation and admitted to the National Women's Health, Auckland City Hospital neonatal intensive care unit (NICU) from July 2005 to October 2008. Infants were excluded if

CRIB II	Clinical Risk Index in Babies 2
NICU	Neonatal intensive care unit

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they were admitted to the NICU after 24 hours of age, died or were discharged before day 7, or had a significant congenital abnormality.

The usual clinical practice during the study period was to start intravenous 10% dextrose at 60-90 mL/kg/day as soon as possible after birth. Standardized amino acid solutions were introduced once central venous access was obtained and increased gradually over the first week. Maternal expressed breast milk was the preferred enteral feeding and was introduced as soon as available. Enteral feeds were increased at up to 30 mL/kg/day. Hyperglycemia was managed by reducing the glucose infusion rate or initiation of an insulin infusion to maintain blood glucose concentration of 72-180 mg/dL (4-10 mmol/L).

Intrauterine growth was determined using birth weight *z*-scores.[22] Maternal ethnicity was prioritized[23] and socioeconomic status determined from maternal address (quintile 5 is most deprived).[24]

All blood glucose concentrations were measured on a blood gas analyzer (ABL 700, Radiometer Ltd, Copenhagen, Denmark), and recorded from birth until the end of postnatal day 7. For 8 participants, blood glucose concentrations measured before NICU admission were also collected (<0.01% of all blood glucose concentrations). Infants with <3 recorded blood glucose concentrations were excluded. All available blood glucose concentrations for each infant were log-transformed to approximate a normal distribution, the mean and standard deviation of the mean calculated, and back-transformed to give a mean blood glucose concentration and a measure of glucose variability.

To determine the effect of absolute glycemia on outcomes, infants were categorized by the occurrence of absolute glycemic excursions during the first week after birth as follows: normoglycemic (a single blood glucose concentration of 38-45 mg/dL [2.1-2.5 mmol/L], or a single blood glucose concentration of 155-180 mg/dL [8.6-10.0 mmol/L], with all other measures 47-153 mg/dL [2.6-8.5 mmol/L]); hypoglycemic (blood glucose concentration of ≤45 mg/dL [2.5 mmol/L] on ≥2 measures >1 hour apart, or any blood glucose concentration ≤36 mg/dL [2.0 mmol/L]); hyperglycemic (blood glucose concentration ≥155 mg/dL [8.6 mmol/L] on ≥2 measures >1 hour apart, or any blood glucose concentration ≥182 mg/dL [10.1 mmol/L]); unstable (≥1 blood glucose concentration ≤45 mg/dL [2.5 mmol/L] and ≥1 blood glucose concentration ≥155 mg/dL [8.6 mmol/L]).

During the study period, written guidelines to guide practice used these blood glucose concentration thresholds, based on the limited data available.[8,13] Glycemic categories were thus defined to reflect clinical practice, aiming to identify infants in whom treatment of glucose excursions was most likely to have taken place. Infants who experienced a single blood glucose concentration slightly outside the normal range were unlikely to have been treated and were therefore included in the normoglycemic group.

Neonatal morbidity and mortality up to 2 years of age were obtained from the clinical records. Survival without neonatal morbidity was defined as the absence of any of death, chronic lung disease,[25] retinopathy of prematurity (grade 3 or 4),[26] intraventricular hemorrhage (grade III or IV),[27] necrotizing enterocolitis (Bell stage ≥2),[25] or periventricular leukomalacia.[25]

Findings were obtained from routine developmental surveillance at 2 years, including Bayley II or Bayley III assessment. Where standardized assessment was not performed, information was obtained from the child's usual doctor. Development was categorized as normal, mild impairment (motor score <-1 SD), moderate impairment (cognitive score -1 to -2 SD or mild-moderate cerebral palsy without cognitive impairment or impaired vision requiring spectacles or conductive hearing loss requiring aids), or severe impairment (cognitive score <-2 SD or severe cerebral palsy or bilateral blindness or sensorineural hearing loss requiring hearing aids).[28]

Statistical Analyses

Data were analyzed using JMP V10 (SAS Institute, Cary, North Carolina). Glycemic groups were compared using ANOVA with the Tukey post hoc correction for multiple comparisons, or Wilcoxon rank-test with Dunn's post hoc test. Categorical data were analyzed using the χ^2 test. Logistic or linear regression were used to investigate relationships between glycemia category, mean blood glucose concentration, glucose variability, and neonatal and 2-year outcomes. Variables where $P < .1$ in bivariate analyses (gestational age, birth weight, birth weight *z*-score, ethnicity, socioeconomic quintile, and Clinical Risk Index in Babies 2 [CRIB II] score[29]) were considered for inclusion in a multivariable model. After assessment for collinearity, variables included in the final multivariable model were gestational age, birth weight *z*-score, and socioeconomic quintile. Relationships between measures of neonatal glycemia and outcome at 2 years of age were additionally adjusted for the type of assessment performed at 2 years of age (Bayley II, Bayley III, other). Data are presented as n (%), median (range), or OR and 95% CI.

Ethical approval was obtained from the Northern B ethics committee (NTY/12/05/035) and institutional approval from the Auckland District Health Board (ADHB 5486).

Results

During the study period, 536 eligible infants were admitted to the NICU, of whom 443 (83%) had glucose profiles available for analysis and 346 (65%) had a 2-year developmental assessment available (**Figure**).

Of participants whose glucose profiles were available for analysis, 287 of the 443 (65%) were categorized as normoglycemic (**Table I**). Infants in the hypoglycemic category (42/443, 9%) were of similar gestational age and birth weight to those in the normoglycemic category. Infants in the hyperglycemic category (73/443, 16%) were of lower gestational age, lower birth weight, and had higher CRIB II scores than those in both the normoglycemic and hypoglycemic categories. Infants in the unstable category (41/443, 9%) were similar to hyperglycemic infants in gestational age and CRIB II score, but had lower birth weights than infants in all other