Infectious disease-related differences in the adaptation of glucose metabolism to fasting in children and the effect of age
Zijlmans, C.W.R.

Citation for published version (APA):
Fasting predisposes to hypoglycemia in Surinamese children with severe pneumonia and very young children are more at risk

Wilco C.W.R. Zijlmans¹, Anne A.M.W. van Kempen², Michael W.T. Tanck³, Mariëtte T. Ackermans⁴, Jeetendra Jitan⁵ and Hans P. Sauerwein⁶.

1 Department of Pediatrics, Diakonessen Hospital, Paramaribo, Suriname, 2 Department of Pediatrics, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands, 3 Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center Amsterdam, The Netherlands, 4 Department of Clinical Chemistry, Laboratory of Endocrinology and Radiochemistry, Academic Medical Center, Amsterdam, The Netherlands, 5 Department of Public Health, Ministry of Health, Paramaribo, Suriname, 6 Metabolism Unit, Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands

Submitted
SUMMARY

OBJECTIVE To investigate the influence of fasting and age on glucose kinetics in children with severe pneumonia.

METHODS Plasma glucose concentration, endogenous glucose production and gluconeogenesis were measured in 12 Surinamese children (six young: 1-3 years, six older: 3-5 years) with severe pneumonia during a controlled 16 hour fast using stable isotopes [6,6-2H2]glucose and 2H2O at a hospital-based research facility.

RESULTS On admission mean glucose concentrations were comparable in both groups: young children: 5.1 ± 1.3 mmol/l, older children: 4.8 ± 0.6 mmol/l, \( P = 0.685 \), and decreased during the first 8 hours of fasting in the young children only: to 3.6 ± 0.5, \( P = 0.04 \) versus 4.2 ± 0.6 mmol/l, \( P = 0.08 \). Glucose production was comparable in both groups: young: 24.5 ± 8.3, older: 24.9 ± 5.9 µmol/kg•min, \( P = 0.926 \). Between 8 and 16 hours of fasting glucose concentration decreased comparably in both groups (young: -0.9 ± 0.7, \( P = 0.004 \), older: -1.0 ± 0.4 mmol/l, \( P = 0.001 \), as did glucose production (young: -6.8 ± 6.3 \( P = 0.003 \), older: -5.3 ± 3.4 µmol/kg•min), \( P = 0.001 \). Gluconeogenesis decreased in young children only: -5.0 ± 7.4, \( P = 0.029 \) versus -1.0 ± 4.7 µmol/kg•min, \( P = 0.609 \).

CONCLUSIONS Like in malaria, fasting predisposes to hypoglycemia in children with severe pneumonia, but its mechanism differs from that in malaria. Young children are more at risk than older children.
INTRODUCTION

Both hypoglycemia and hyperglycemia are common and serious complications in severely ill children (1-3). In Kenyan children hypoglycemia occurs frequently in malaria (8.4%), pneumonia (3.9%) and diarrhea (5.5%). The overall mortality is 20.2% in children with hypoglycemia compared to 3.8% in normoglycemic children (2), making these three diseases major killers in the tropics (4-8). In Tanzanian children the frequency of hypoglycemia did not differ between malaria (5.2%) and other serious illnesses (11.2%) (4).

Hypoglycemia is particularly common in young children below the age of 3 years (2,9). We previously showed that young children (< 3 years) with uncomplicated malaria had a higher risk of developing hypoglycemia than older children (3-5 years): after a controlled 8 hour fast plasma glucose concentration was lower in children < 3 years than in children 3 – 5 years of age (median 5.0 (range 4.0 - 5.5) mmol/l versus 5.4 (4.8 - 6.1) mmol/l, p = 0.028), whereas endogenous glucose production was comparable in both groups (10).

Several studies show an association between hypoglycemia and the time since the last meal (4,8), suggesting that hypoglycemia in severely ill children is not a specific feature of disease, but merely a consequence of fasting. This was confirmed in our study on glucose kinetics in young Surinamese children with severe and non-severe malaria (11).

Data on glucose kinetics during fasting in children are scarce. So far, a limited number of studies performed direct measurements of endogenous glucose production and gluconeogenesis in children under five years of age with malaria and idiopathic ketotic hypoglycemia (10-15) and in older healthy obese and normal prepubertal children (16-18). There are no data on glucose kinetics during fasting in children with pneumonia.

We hypothesize that hypoglycemia in children with severe pneumonia is due to prolonged fasting and younger children are more at risk than older children. The primary objective of this study was to measure the influence of a prolonged period of controlled fasting and age on the plasma glucose concentration, endogenous glucose production and the contribution of gluconeogenesis in children with severe pneumonia under the age of five in Suriname.

SUBJECTS AND METHODS

Patients

All children between 1 and 5 years of age with a primary diagnosis of pneumonia and necessity of intravenous antibiotic therapy, who were admitted during the 16 month study period (lasting from October 2006 to February 2008) to the Diakonessen Hospital in Paramaribo, were eligible for inclusion in the study.

The diagnosis severe pneumonia was defined according to WHO guidelines (19): cough or difficult breathing with respiratory distress (lower chest wall retractions or abnormally deep
breathing), tachypnoe (≥ 40 breaths per minute) and chest auscultation signs (decreased breath sounds, bronchial breath sounds, crackles, abnormal vocal resonance, pleural rub). Exclusion criteria were: plasma glucose concentration < 3.0 mmol/l on admission, very severe pneumonia according to the WHO criteria (central cyanosis, inability to drink or profound vomiting, convulsions, lethargy or unconsciousness, severe respiratory distress, or X-ray signs of pleural effusion, empyema, pneumothorax, pneumatocele and interstitial pneumonia) (19), need for mechanical ventilation, severe anemia (hemoglobin concentration < 3.5 mmol/l (63 mg/dl), severe acidosis (pH < 7.25), severe chronic diarrhea, documented malaria, documented endocrinological disease and concomitant infectious diseases.

Nutritional status was assessed by weight for length/height on the WHO Child Growth Standards for children less than five years of age (20). The time the children had their last meal or drink either at home or in the hospital was recorded and considered as the start of the fasting period prior to the study.

All severely ill children admitted at the Diakonessenhuis Hospital are treated according to the guidelines of proper pediatric intensive care medicine. In case of respiratory or circulatory insufficiency and in case of metabolic dysregulation this is promptly corrected.

Written informed consent was obtained from the accompanying parent or guardian. This study was approved by the Suriname National Ethical Committee.

Study design

After admission, patients were stabilized and recruited immediately after radiodiagnostic confirmation of the clinical diagnosis. Basal hematological and biochemical parameters were measured for clinical purposes. Patients were treated with intravenous ampicillin. An intravenous cannula was introduced in a peripheral vein for clinical reasons (IV therapy) and also used for stable isotope infusion. A second cannula for blood sampling was introduced into a suitable vein in the contralateral arm or foot. Both cannula’s were introduced after Emla® cream application for local anesthesia. Blood sampling from the venous catheter proved to be technically possible and was tolerated well by all children. Whenever possible, blood samples for study purposes were tied with samples for clinical reasons. The catheters were kept patent by a slow isotonic saline drip.

The study design is shown in figure 1. After obtaining a baseline blood sample at t = -8.15 hr for determination of background isotopic abundance and plasma glucose, the patients were given 1 g of 2H2O per kg body water at 30-minute intervals for a total of five times (total dose of 5 g/kg body water). Body water was estimated to be 60% of body weight both for boys and girls. The patient was fasted until the end of the study but was allowed to drink water ad libitum, enriched 0.5% with 2H2O, in order to maintain isotopic steady state.

At t = -2.15 hr a blood sample was drawn for plasma glucose concentration and enrichment of [6,6-2H2]glucose. Immediately thereafter a primed (3.2 mg/kg), continuous (2.4 mg/kg•h or 0.33 µmol/kg•min) infusion of [6,6-2H2]glucose (Cambridge Isotope
Figure 1 Study design.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Admission</th>
<th>-8</th>
<th>-6</th>
<th>-4</th>
<th>-2</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
</table>

Blood samples

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>XXX</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>XXX</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bedside glucose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enrichment</td>
<td>Background</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[6,6-^2H_2]glucose</td>
<td>X</td>
<td>XXX</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>^2H at glucose C5</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormones</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Laboratories, Andover MA, USA) dissolved in sterile isotonic saline and sterilized by passage of the solution through a millipore filter was administered by a motor-driven, calibrated syringe pump (Perfusor® Secura FT, B.Braun, Germany). At t = -0.15 hr (8 hrs of controlled fasting) three blood samples were collected at intervals of 5 minutes for the measurement of isotopic enrichment and plasma glucose concentration. Between t = 0 hr and t = 8 hr (16 hrs of controlled fasting, end of the study) blood samples for plasma glucose concentration and enrichment of [6,6-^2H_2]glucose were obtained every hour. Blood samples for ^2H-enrichment in glucose (at the C5 position) and deuterium enrichment in body water were drawn at t = -8, t = 0 and t = 8 hr. Blood samples for determination of plasma concentration of insulin, counterregulatory hormones and FFA were collected at t = 0 hr and t = 8 hr.

Safety measures

Hypoglycemia was defined as a plasma glucose concentration below 2.5 mmol/l. Children with a plasma glucose concentration <3.0 mmol/l on admission were excluded from the study, because of the risk of developing hypoglycemia during the planned fasting period. In order to detect hypoglycemia without delay, glucose concentrations were checked at 4-hour intervals during the entire study using a bedside point of care device (Precision Q•I•D, MediSense Inc., II, USA) in addition to the glucose measurements on admission and samples taken for the study. In case of a glucose concentration < 2.5 mmol/l or clinical symptoms of hypoglycemia, the study would be terminated and the patient would be promptly treated. The maximum amount of blood to be taken for study purposes was set at 5 ml/kg body weight with a maximum absolute amount of 31.0 ml for the entire study. Haemoglobin concentration was checked after the study.
Assays

Blood for measurement of gluconeogenesis was promptly deproteinized by adding an equal amount of 10% perchloric acid. Blood for [6,6-$^2$H$_2$]glucose enrichment, deuterium enrichment in body water as well as hormones was collected in prechilled heparinized tubes. All samples were kept on ice and centrifuged immediately. Plasma was stored at -20°C and was transported on dry ice before assay in the Netherlands.

Plasma samples for glucose enrichments of [6,6-$^2$H$_2$]glucose were deproteinized with methanol (21). The aldonitril penta-acetate derivative of glucose was injected into a gas chromatograph/mass spectrometer system. Separation was achieved on a J&W (J&W Scientific, FOL, CA, USA) DB17 column (30 m x 0.25 mm, d$_f$ 0.25 µm). Glucose was monitored at m/z 187, 188 and 189. The enrichment of [6,6-$^2$H$_2$]glucose was determined by dividing the peak area of m/z 189 by the peak area of 187 and correcting for natural enrichments. Glucose concentrations were determined on a Biosen C-line glucose analyser (EKF diagnostics, Barleben/Magdeburg, Germany).

To measure deuterium enrichment at the C5 position, glucose was converted to hexamethylenetetraamine (HMT) as described by Landau et al. (22) and Ackermans et al. (23). HMT was injected into a gas chromatograph mass spectrometer. Separation was achieved on an AT-Amine (Alltech, Deerfield, IL, USA) column (30 m x 0.25 mm, d$_f$ 0.25 µm). HMT consists of six formaldehyde molecules, originally derived from the C5 of six glucose molecules (intra-assay coefficient of variation (c.v.) for deuterium enrichment at the C5 position: 8.5%, inter-assay c.v.: 10%).

Deuterium enrichment in body water was measured by a method adapted from Previs et al. (24) intra-assay c.v. for deuterium enrichment in body water: 6%, inter-assay c.v.: 6%).

All isotopic enrichments were measured on a gas chromatograph mass spectrometer (model 6890 gas chromatograph coupled to a model 5973 mass selective detector, equipped with an electron impact ionisation mode, Hewlett-Packard, Palo Alto, CA).

Cortisol and insulin were measured in an Immulite 2000 system (Diagnostic Products Corporation, Los Angeles, USA). Cortisol was determined with a chemiluminiscent immunoassay (intra-assay variation 89 nmol/l 8%, 500 nmol/l 7%; inter-assay variation 136 nmol/l 8%, 1092 nmol/l 7%; detection limit 50 nmol/l) and insulin was determined with a chemiluminiscent immunoassay (intra-assay variation 47 pmol/l 6%, 609 pmol/l 3%; inter-assay variation 91 pmol/l 4%, 120 pmol/l 6%; detection limit 15 pmol/l).

Glucagon was determined by RIA (Linco Research, St. Charles, MO, USA), intra-assay c.v.: 3-5 %, inter-assay c.v.: 9-13 %, detection limit: 15 ng/l. Norepinephrine and epinephrine were determined by an in-house HPLC method. Norepinephrine: intra-assay c.v.: 6-8 %, inter-assay c.v.: 7-10 %, detection limit: 0.05 nmol/l. Epinephrine: intra-assay c.v.: 6-8 %, inter-assay c.v. 7-12 %, detection limit: 0.05 nmol/l. Plasma free fatty acids were measured by an enzymatic method (NEFAC; Wako chemicals GmbH, Neuss, Germany), intra-assay c.v. 2-4 %, inter-assay c.v.: 3-6 %, detection limit: 0.02 mmol/l.
Calculations

Endogenous glucose production was calculated from the dilution of labelled glucose in plasma. Because plasma glucose concentrations and tracer/tracer ratios for [6,6-\textsuperscript{2}H\textsubscript{2}] glucose were constant during each sampling phase of the study, calculations for steady state kinetics were applied, adapted for the use of stable isotopes (25). The rate of gluconeogenesis was calculated by multiplication of the EGP by fractional gluconeogenesis. The fractional gluconeogenesis (\%) \(= 100 \times \left( {^{2}\text{H}} \right. \text{enrichment on C5 of glucose} \div \left( {^{2}\text{H}} \right. \text{enrichment in total body water}) \).

Statistics

Normally distributed variables (Shapiro-Wilk statistic > 0.9) are presented as means ± SD. Other variables are presented as median with range (min – max). Differences between the young and the older group in clinical and laboratory data on admission were analyzed by the Mann-Whitney test, differences in glucose kinetics at \( t = 0 \) were analyzed by the \( t \)-test for independent variables. Differences between age groups in the change of hormones and FFA after 8 hours and after 16 hours of fasting were analyzed by Mann-Whitney test, whereas changes within age groups were analyzed using the Wilcoxon signed ranks test (paired data). To investigate the influence of fasting duration and age on plasma glucose concentration and EGP, a repeated measurements analysis of variance (SPSS version 16.0) was used with time as a linear variable. To investigate after how much time the young and older children would become hypoglycemic, extrapolation of the plasma glucose concentration values was performed, assuming that the decrease of plasma glucose concentration was linear in time in both groups. Statistical significance was set at \( p < 0.05 \).

RESULTS

Clinical data

Clinical and laboratory details are given in table 1. Twelve Surinamese children under the age of five years with severe pneumonia were studied: 6 children were younger than 3 years and 6 children were between 3 and 5 years of age. There were no differences in any of the clinical and biochemical characteristics between the groups and all values of biochemical characteristics were within the reference range for age. None of the children needed a blood transfusion before entering the study and none of them had a decline in Hb greater than 0.5 mmol/l after the study. All patients responded well to therapy and made uneventful recoveries. None of the children experienced any side effects (specifically: nausea or vertigo) from the deuterated water.
Basal glucose kinetics

Mean plasma glucose concentration on admission was similar in both groups: young children: 5.1 ± 1.3 mmol/l, older children: 4.8 ± 0.6 mmol/l, P = 0.685 (table 1). During the first eight hours of controlled fasting mean plasma glucose concentration declined significantly in the young children: -1.4 ± 1.4 mmol/l (P = 0.04), and in the older children: -0.6 ± 0.7 mmol/l, although this decline was not significant (P = 0.08) (figure 2). After 8 hours of controlled fasting (t = 0) the mean plasma glucose concentration was lower in the young children than in the older children (P = 0.038). All other parameters of glucose kinetics were comparable in the young and older children (table 2).

Glucose kinetics during extended fasting

Figure 2 shows the plasma glucose concentration on admission and during controlled fasting. Between 8 and 16 hours of fasting plasma glucose concentration decreased significantly over time in both groups: younger group -0.9 ± 0.7 mmol/l, P = 0.004, older group -1.0 ± 0.4 mmol/l, P = 0.001. There was no difference in the rate of decline between the groups (P = 0.709). Two young children and one older child developed hypoglycemia with plasma glucose < 2.5 mmol/l (2.1, 2.3 and 2.1 mmol/l respectively) at the end of the study (after 16 hours of controlled fasting); they were given proper treatment immediately. None of the children had clinical symptoms of hypoglycemia.

Figure 3 shows endogenous glucose production between 8 and 16 hours of fasting. EGP decreased significantly over time in both groups: younger group: -6.8 ± 6.3 µmol/kg•min,

<table>
<thead>
<tr>
<th>Table 1 Clinical and biochemical characteristics on admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 years (n = 6)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Fasting prior to study (hr)</td>
</tr>
<tr>
<td>Weight for length/height (SD)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
</tr>
<tr>
<td>Glucose concentration on admission (mmol/l)</td>
</tr>
<tr>
<td>Haemoglobin (mmol/l)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
</tr>
<tr>
<td>Capillary PH</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
</tr>
<tr>
<td>Serum AST (U/l)</td>
</tr>
<tr>
<td>Serum ALT (U/l)</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
</tr>
</tbody>
</table>

Normally distributed data are presented as means ± SD, other data as median with range.
Figure 2 Plasma glucose concentration on admission (= start of controlled fast) and between 8 and 16 hours of controlled fasting in young (< 3 years) and older (3-5 years) children with severe pneumonia. Regression equation young group: plasma glucose concentration = 3.6215 – (0.1155 × time); older group: plasma glucose concentration = 4.0927 – (0.1225 × time). Data are means ± SEM.

Table 2 Glucose kinetics after 8 hours of controlled fasting (t=0)

<table>
<thead>
<tr>
<th></th>
<th>&lt; 3 years</th>
<th>3-5 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose concentration (mmol/l)</td>
<td>3.6 ± 0.5</td>
<td>4.2 ± 0.3</td>
<td>0.038</td>
</tr>
<tr>
<td>Glucose production (µmol/kg•min)</td>
<td>24.5 ± 9.0</td>
<td>24.9 ± 6.4</td>
<td>0.926</td>
</tr>
<tr>
<td>Gluconeogenesis (µmol/kg•min)</td>
<td>17.5 ± 6.7</td>
<td>14.7 ± 2.8</td>
<td>0.383</td>
</tr>
<tr>
<td>Glycogenolysis (µmol/kg•min)</td>
<td>7.1 ± 5.4</td>
<td>10.3 ± 5.5</td>
<td>0.334</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.

\[ P = 0.003, \text{ older group: } -5.3 \pm 3.4 \ \mu\text{mol/kg\cdot min}, \text{ } P = 0.001. \] There was no difference in the rate of decline between the groups (\( P = 0.451 \)).

Gluconeogenesis decreased between 8 and 16 hours of fasting in the young children from 17.5 ± 6.7 to 12.5 ± 4.7 \( \mu \text{mol/kg\cdot min} \), \( P = 0.029 \), but remained stable in the older children: 14.7 ± 2.8 and 13.7 ± 5.0 \( \mu \text{mol/kg\cdot min} \) (\( P = 0.609 \)). The contribution of gluconeogenesis to endogenous glucose production did not change in either group: young children: 72 ± 15 and 69 ± 15 % (\( P = 0.956 \)), older children: 61 ± 14 and 69 ± 9 % (\( p = 0.178 \)). There were no difference between the groups after 8 and after 16 hours of fasting: \( P = 0.227 \) and \( P = 0.970 \) respectively.
Glycogenolysis did not change in the young children between 8 and 16 hours of fasting: 7.1 ± 5.4 and 5.2 ± 2.3 µmol/kg•min (\(P = 0.239\)), but decreased in the older children from 10.3 ± 5.5 to 6.0 ± 2.6 µmol/kg•min, \(P = 0.035\).

Glucoregulatory hormones and free fatty acids

Table 3 Glucoregulatory hormones and free fatty acids after 8 hours and after 16 hours of fasting

<table>
<thead>
<tr>
<th></th>
<th>&lt; 3 years (n = 6)</th>
<th>3-5 years (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 hr fast</td>
<td>16 hr fast</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>7.5 (7.5-7.5)</td>
<td>7.5 (7.5-7.5)</td>
</tr>
<tr>
<td>Glucagon (ng/l)</td>
<td>79 (69-108)</td>
<td>97 (55-151)</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>513 (328-1418)</td>
<td>679 (450-1402)</td>
</tr>
<tr>
<td>Epinephrine (nmol/l)</td>
<td>0.06 (0.05-1.81)</td>
<td>0.23 (0.05-1.63)</td>
</tr>
<tr>
<td>Norepinephrine (nmol/l)</td>
<td>0.26 (0.21-1.72)</td>
<td>0.54 (0.20-1.83)</td>
</tr>
<tr>
<td>FFA (mmol/l)</td>
<td>0.97 (0.78-2.69)</td>
<td>1.16 (0.91-3.3)</td>
</tr>
</tbody>
</table>

Data are median with range. \(\dagger P = 0.028\) and \(\dagger\dagger P = 0.046\) for comparison within < 3 years group.

Glycogenolysis did not change in the young children between 8 and 16 hours of fasting: 7.1 ± 5.4 and 5.2 ± 2.3 µmol/kg•min (\(P = 0.239\)), but decreased in the older children from 10.3 ± 5.5 to 6.0 ± 2.6 µmol/kg•min, \(P = 0.035\).

Glucoregulatory hormones and free fatty acids

Data are shown in Table 3. Between 8 and 16 hours of fasting norepinephrine and free fatty acid concentrations increased only in the younger children (\(P = 0.028\) and \(P = 0.046\) resp.). The plasma concentration of the other glucoregulatory hormones and the free fatty acids did not change significantly over time and there were no differences between the groups.
DISCUSSION

This is the first study on glucose kinetics in children with severe pneumonia under the age of five during a 16 hour period of controlled fasting. It shows that both fasting and age are important factors in the development of hypoglycemia in these children. On admission the plasma glucose concentration was comparable in both groups and decreased only in the young children during the first 8 hours of fasting. Between 8 and 16 hours of fasting, the plasma glucose concentrations decreased comparably in both groups, indicating that the age difference in the rate of decline of plasma glucose exists only in the early few hours of the fast. In other words glucose metabolism in children < 3 years adapts adequately albeit slower to fasting than in older children. With the assumption that the decrease of plasma glucose concentration between 8 and 16 hours of fasting was linear in time in both groups, linear regression analysis using a mixed linear model, showed that hypoglycemia (plasma glucose < 2.5 mmol/l) would occur after 18 hours of fasting in the young children and after 21 hours in the older children (P = 0.041). The fasting period prior to the study is of influence but this period was similar for both groups. Adding this pre-study fasting duration, young children with severe pneumonia become hypoglycemic after 25 hours and older children after 27 hours of fasting. Therefore we conclude that prolonged fasting is an important risk factor for hypoglycemia in young children with severe pneumonia, mainly due to a less adequate metabolic adaptation to fasting in the first 15 hours. Our findings are in line with the literature that states that hypoglycemia is not a specific feature of disease, but is considered the consequence of prolonged fasting in ill children (2,4,5,8,9,11,26-29).

Published data on glucose production in young children with severe pneumonia and its relation with fasting duration are lacking. After the first 8 hours of fasting EGP was not different between groups, although the plasma glucose concentration was lower in the young children. Between 8 and 16 hours of fasting the decline in endogenous glucose production and plasma glucose concentration in the young children was parallel to the decline in older children. In adults, between 10 and 16 hours of fasting, glucose production declines by ~ 20%, with a minimal change in glucose concentration, indicating that the mechanism of maintenance of plasma glucose concentration during fasting is mainly via a reduction in peripheral utilization (30,31). In the present study in children with pneumonia the decline in plasma glucose concentration and in endogenous glucose production were positively correlated (R-Square 0.40, P < 0.001) between 8 and 16 hours of fasting. This indicates that glucose production is an important determinant of glucose concentration in children with pneumonia during fasting. This relationship was also found in Kenyan children with uncomplicated malaria (12). Our data therefore suggest that, in general, children with infectious disease are less able to reduce glucose utilization than adults during fasting. Absolute gluconeogenesis decreased in all young children over time, but its contribution to glucose production did not change. In the older children absolute gluconeogenesis
also decreased in all children except for one child, which precluded the change to be statistically significant. We therefore have reservations about possible age-related differences in gluconeogenesis or precursor supply as the explanation for hypoglycemia in young children (32-34). However, these findings in children with pneumonia are remarkable since in children with malaria absolute gluconeogenesis does not change and fractional gluconeogenesis increases after extended fasting (11). A possible explanation for this difference are the glucagon and insulin concentration: in children with malaria the glucagon concentration increases and insulin concentration decreases during extended fasting, whereas it remains stable in the children with pneumonia in the present study. This observation suggests the existence of infectious disease related differences in hormonal response during fasting in children. Our data cannot be compared with literature due to lack of publications on this issue.

We conclude that fasting is a significant determinant of plasma glucose concentration. During fasting young children with severe pneumonia below 3 years of age initially have a higher risk for developing hypoglycemia than older children in spite of high plasma concentrations of glucoregulatory hormones and free fatty acids. This is due to a slower rate of reducing glucose utilization than in older children. After prolonged fasting the risk of hypoglycemia concerns children 3-5 years of age as well. There may also be an effect of the kind of infectious disease on the adaptation of glucose metabolism during fasting in children. Further studies are needed to elucidate its pathophysiological mechanism.
REFERENCES

    concentrations on admission to a rural Kenya district hospital: prevalence and outcome. Arch Dis Child
    88:621-625
    83:S46-553
    paediatric admissions in Mozambique. Lancet 343:149-150
    African children with severe malaria. Lancet 1:708-711
7. English M, Wale S, Binns M, Mwangi I, Sauerwein H, Marsh K 1998 Hypoglycaemia on and after admis-
    sion in Kenyan children with severe malaria. QJM 91:191-197
    J Trop Pediatr 52:96-102
    young children with uncomplicated falciparum malaria have higher risk of hypoglycemia: A study from
    Suriname. Trop Med Int Health 13:626-634
    during fasting in young Surinamese children with severe and non-severe falciparum malaria. Am J Trop
    Med Hyg 79:605-612
    Marsh K, Sauerwein HP 1996 The relationship between glucose production and plasma glucose concen-
    K, Sauerwein HP 1997 The influence of alanine infusion on glucose production in ‘malnourished’ Afri-
    can children with falciparum malaria. QJM 90:455-460
    Glucose homeostasis in children with falciparum malaria: precursor supply limits gluconeogenesis and
    glucose production. J Clin Endocrinol Metab 82:2514-2521
15. Huidekoper HH, Duran M, Turkenburg M, Ackermans MT, Sauerwein HP, Wijburg FA 2008 Fasting
    adaptation in idiopathic ketotic hypoglycemia: a mismatch between glucose production and demand.
    Eur J Pediatr 167:859-865
    Am J Physiol 271:E814-E820
17. Sunehag AL, Treuth MS, Toffolo G, Butte NF, Cobelli C, Bier DM, Hamond MW 2001 Glucose produc-
    tion, gluconeogenesis, and insulin sensitivity in children and adolescents: an evaluation of their repro-
   ducibility. Pediatr Res 50:115-123
    macronutrient content on glucose metabolism in children. J Clin Endocrinol Metab 87:5168-5178

Glucose kinetics in children with severe pneumonia


