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

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Chapter 4

Glucose kinetics during fasting in young children with severe and non-severe malaria in Suriname

Wilco Zijlmans, Anne van Kempen, Mariëtte Ackermans, Jesse de Metz, Piet Kager, and Hans Sauerwein.

Department of Pediatrics, Diakonessen Hospital, Paramaribo, Suriname; Department of Pediatrics, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; Department of Clinical Chemistry, Laboratory of Endocrinology and Radiochemistry; Department of Intensive Care Medicine; Department of Infectious diseases, Tropical Medicine and AIDS; Metabolism Unit, Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands
ABSTRACT

Fasting could be an important factor in the induction of hypoglycemia in children with malaria, because fasting results in a decline in endogenous glucose production. The influence of extended fasting on plasma glucose concentration, glucose production and gluconeogenesis were measured using [6,6-2H2]glucose and 2H2O in 12 Surinamese children with severe malaria and compared with 16 children with non-severe malaria during a 16 hour controlled fast. Glucose concentration and glucose production were comparable after 8 hours of fasting and decreased in both groups (p < 0.001) with an extension of the fast up to 16 hours. Glucose concentration decreased faster in the non-severe group than in the severe group (p = 0.029). The decrease in glucose production was not different between groups (p = 0.954). Conclusion: fasting predisposes for hypoglycemia in young children with falciparum malaria. Hypoglycemia due to fasting develops later in young children with severe malaria than in children with non-severe malaria.
INTRODUCTION

Hypoglycemia is a common and serious complication in children with severe malaria, and it also predicts mortality.\(^1,2\) Hypoglycemia occurs more frequently in children (up to 25%)\(^3\text{--}^6\) than in adults (8%).\(^7\) The pathogenesis of hypoglycemia in malaria is still incompletely understood. There are several generally accepted risk factors, like prolonged fasting, severity of the infection, young age and malnutrition.\(^8\text{--}^16\)

Fasting is considered a risk factor because it leads to glycogen depletion, which can result in decreased glucose production and hypoglycemia.\(^8,17,18\) Healthy adults are able to maintain normal plasma glucose levels up to 86 hours of fasting.\(^9\) Healthy children however are not able to maintain a normal plasma glucose concentration during a fasting period of 24 hours and show a significant steeper decrease in plasma glucose concentration than adults.\(^10\text{--}^12\)

In earlier studies we found that infection with \textit{Plasmodium falciparum} resulted in an increase in glucose production in different patient groups, both in non-severe falciparum malaria and in severe falciparum malaria.\(^8,13,14,19\) In adults with non-severe malaria glucose production increased 20% compared with healthy controls.\(^8,19\) In adults with severe malaria and adults with cerebral malaria glucose production was doubled.\(^14,20\)

In pregnant women, infection with \textit{Plasmodium falciparum} resulted in higher glucose production and higher glucose concentrations during 24 hours of fasting, thereby delaying the occurrence of hypoglycemia.\(^8\) There are few studies of glucose production in young children with malaria. In older children with non-severe malaria endogenous glucose production proved to be a significant determinant of plasma glucose concentration.\(^21\) Other studies show that glucose production was higher in children with severe malaria than with non-severe malaria.\(^22,23\) There are no studies comparing glucose kinetics in children with severe malaria and non-severe malaria during a controlled and objectively observed fasting period.

Hypoglycemia is particularly common in young children with falciparum malaria below the age of 3 years.\(^3,15\) Since glycogen stores in the young child are limited, a period of prolonged fasting could be a major risk factor for hypoglycemia. Nutritional status is of influence on glucose production but data in children are limited and contradictory.\(^16,23,24\)

We hypothesized that prolonged fasting is an important determinant in the development of hypoglycemia in children with falciparum malaria, and that children with severe malaria are more at risk than children with non-severe malaria.

The primary objective of this study was to measure the influence of a prolonged period of controlled fasting on the plasma glucose concentration, endogenous glucose production (EGP) and the contribution of gluconeogenesis in children with severe malaria and non-severe malaria in Suriname.
MATERIALS AND METHODS

Patients.

All children admitted during the 2.5 year study period to the Diakonessen Hospital in Paramaribo, which is the main referral hospital for the interior of Suriname, with a primary diagnosis of falciparum malaria and plasma glucose concentrations at admission of \( \geq 3.0 \) mmol/L were eligible for inclusion in the study. Six children with non-severe malaria were studied at Distrikt Hospital Stoelmanseiland in the interior of Suriname.

Exclusion criteria were: plasma glucose concentration < 3.0 mmol/L, treatment with quinine or other well-known stimulators of insulin secretion, severe chronic diarrhea, documented endocrinological disease and concomitant infectious diseases. Children were considered to have severe malaria according to the WHO criteria: if > 2% of erythrocytes were infected, in case of severe anemia (haemoglobin < 5.0 g/dL or 3.1 mmol/L), hypoglycemia (plasma glucose concentration < 3.0 mmol/L, in that case the patient would be excluded), if they were prostrated or in respiratory distress, in case of impaired consciousness, multiple convulsions within the past 24 hours, or if they had (other) signs of cerebral malaria (Blantyre coma score \( \leq 2 \)) \(^{15}\) which was not attributable to any other cause. All patients with suspected cerebral malaria had a lumbar puncture to exclude other causes of coma. Patients with non-severe malaria were defined as having < 2% of erythrocytes infected and none of the above mentioned criteria.

All severely ill children admitted at the Diakonessenhuis Hospital were 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 was promptly corrected. Patients with hypoglycemia were instantly treated and were not eligible for the study.

Patients with a haemoglobin concentration below 3.5 mmol/L were given a blood transfusion of at least 20 ml/kg. If the haemoglobin concentration after the blood transfusion was > 5.0 mmol/l, they were eligible for the study.

Nutritional status was assessed by weight for length/height on the WHO Child Growth Standards for children under five years of age.\(^{25}\) Children with a weight for length/height below -2.0 SD were considered malnourished.

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.

Written informed consent was obtained from the accompanying parent or guardian. This study was approved by the Suriname National Ethical Committee and the Ethical Committee of the Academic Medical Centre, Amsterdam, The Netherlands.

Study design. After admittance, patients were stabilized and recruited immediately after laboratory confirmation of the clinical diagnosis and exclusion of quinine-use by a quinine dipstick.\(^{26}\) Basal hematological and biochemical parameters were measured for clinical purposes.
Patients with non-severe malaria were treated with halofantrine. An electrocardiogram was made to rule out congenital prolonged QT interval (halofantrine would then be contraindicated). Patients with severe malaria were treated with intramuscular artemotil.

An intravenous cannula was introduced in a peripheral vein 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 $^{2}$H$_2$O 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 $^{2}$H$_2$O, 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-$^{2}$H$_2$]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-$^{2}$H$_2$]glucose (Cambridge Isotope 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 = -0.30 hr (7.45 hrs of fasting) three
blood samples were collected at intervals of 15 minutes for the measurement of isotopic enrichment and plasma glucose concentration. Between t = 0 hr and t = 8 hr (16 hrs of fasting, end of the study) blood samples for plasma glucose concentration and enrichment of [6,6-²H₂]glucose were obtained every hour. Blood samples for ²H-enrichment in glucose (at the C₅ position) were drawn at t = -8, t = 0, t = 4 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.

Two major concerns had to be addressed in this study: the risk of hypoglycemia and amount of blood to be sampled. In order to detect hypoglycemia without delay, glucose concentrations were checked hourly during the entire study using a bedside point of care device (Precision Q•I•D, MediSense Inc., IL, USA) in addition to the glucose measurements on admission and samples taken for the study. In case hypoglycemia would occur (blood glucose < 3 mmol/l) the patient would be promptly treated and excluded from further study (however, none of the patients developed hypoglycemia during the study).

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 36.8 ml for the entire study. For that reason, in one child with a body weight of 7.1 kg, only blood samples for glucose concentrations and enrichment were taken (total amount 24.8 ml); samples for hormones, alanine and FFA were omitted. Haemoglobin concentration was checked after a blood transfusion (if applicable) and after the study.

Assays

Blood for measurement of gluconeogenesis was promptly deproteinized by adding an equal amount of 10% perchloric acid. Blood for [6,6-²H₂]glucose enrichment 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 [6,6-²H₂]glucose were deproteinized with methanol.²⁷ 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, dₜ 0.25 µm). Glucose concentrations were determined by gas chromatography using xylose as an internal standard. Glucose was monitored at m/z 187, 188 and 189. The enrichment of [6,6-²H₂] glucose was determined by dividing the peak area of m/z 189 by the peak area of 187 and correcting for natural enrichments.

To measure deuterium enrichment at the C₅ position, glucose was converted to hexamethylenetetramine (HMT) as described by Landau and Ackermans.²⁸,²⁹ 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, dₜ 0.25 µm). HMT
Glucose kinetics in children with severe and non-severe malaria

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 30 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 on 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 immunometric assay (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. Serum 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.

The glucose rate of appearance (Ra) was calculated by the isotope dilution from the [6,6-\(^{2}\text{H}_2\)] enrichment of glucose in plasma, using non steady state equations as described by Steele 31,32: 

\[
Ra = \frac{F - pV \times \left[\frac{(C_2 + C_1)}{2}\right] \times \left[\frac{(E_2 - E_1)}{(t_2 - t_1)}\right]}{(E_2 + E_1) / 2}
\]

where Ra = rate of appearance of glucose (in µmol/kg•min), F = [6,6-\(^{2}\text{H}_2\)]glucose infusion rate (in µmol/kg•min), E = percent of glucose molecules enriched with \(^{2}\text{H}\) (in absolute values), C = plasma glucose concentration (in mmol/L), t = time at the sampling points (in min) and pV = effective distribution volume of glucose, assumed to be 75% of the extracellular water volume. The volume of extracellular water was calculated by normogram from body weight and height.33 To calculate endogenous glucose production rate exogenously infused glucose was subtracted from glucose Ra. The fractional gluconeogenesis (%) = 100 × ([\(^{2}\text{H}\)] enrichment on C5 of glucose/ [\(^{2}\text{H}\)] enrichment in total body water). The rationale for these calculations has been discussed in detail by Landau.28

Statistics. To investigate the influence of fasting duration, severity of infection, age and weight-for-height percentile on plasma glucose concentration and EGP, mixed models
analysis with repeated measurements analysis of variance (SPSS version 12.0.1) was used with time as a linear variable. Since some data of glucose kinetics were not normally distributed, ranks of valuables were used. To investigate after how much time children with severe malaria and non-severe malaria would become hypoglycemic, extrapolation of the plasma glucose concentration was performed using parametric linear mixed model analysis. For each of the models, the residuals were normally distributed (Wilk-Shapiro’s W > 0.95) and showed constant variance. Differences between the severe and the non-severe group in clinical and laboratory data and glucose kinetics at t = 0 were analyzed by the t-test for independent variables, the paired data of hormones and FFA by the paired samples t-test. Data are represented as the median and range unless otherwise stated. Statistical significance was set at p < 0.05.

RESULTS

Clinical data

Clinical and laboratory details are given in table 1. Twenty-eight Surinamese children under the age of five years with acute falciparum malaria were studied: 12 children had severe malaria, 16 children had non-severe malaria. Three children with severe disease had cerebral malaria. The severe malaria children had a longer duration of illness, were more severely anemic, and had higher concentrations of C-reactive protein, aminotransferases, bilirubin and creatinine, all consistent with severe disease.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and biochemical characteristics on admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>severe (n = 12)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>3.3 (1.0--4.8)</td>
</tr>
<tr>
<td>Fasting prior to study (hr)</td>
<td>11 (2--32)</td>
</tr>
<tr>
<td>Weight for length/height (SD)</td>
<td>-0.65 (-3.3--0.7)</td>
</tr>
<tr>
<td>Duration of illness (d)</td>
<td>5 (2--14)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.3 (36.4--39.8)</td>
</tr>
<tr>
<td>Parasitemia (/µl)</td>
<td>174000 (177--495000)</td>
</tr>
<tr>
<td>Haemoglobin (mmol/L) *</td>
<td>3.2 (1.3--6.1)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>101 (31--333)</td>
</tr>
<tr>
<td>Serum AST (U/L)</td>
<td>87 (23--551)</td>
</tr>
<tr>
<td>Serum ALT (U/L)</td>
<td>22 (5--52)</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>19 (7--43)</td>
</tr>
<tr>
<td>Kreatinine (µmol/L)</td>
<td>38 (23--62)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/9</td>
</tr>
</tbody>
</table>

* Patients with a haemoglobin concentration below 3.5 mmol/L on admission were given a blood transfusion. After the transfusion the haemoglobin concentration was > 5.0 mmol/l in all children.
All children with severe anemia had haemoglobin values above 5.0 mmol/l after blood transfusion before entering the study. None of the children had a decline in Hb greater than 0.5 mmol/l after the study.

All patients, including the children with cerebral malaria, responded well to therapy and made uneventful recoveries. None of the children experienced any side effects (specifically: nausea or vertigo) of the deuterated water.

**Basal glucose kinetics**

After 8 hours of controlled fasting, all parameters of glucose kinetics were comparable in severe malaria and non-severe malaria children (table 2).

<table>
<thead>
<tr>
<th>Table 2 Glucose kinetics after 8 hours of fasting. Data are medians and ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Glucose concentration (mmol/L)</td>
</tr>
<tr>
<td>Glucose production (µmol/kg•min)</td>
</tr>
<tr>
<td>Gluconeogenesis (µmol/kg•min)</td>
</tr>
<tr>
<td>Glycogenolysis (µmol/kg•min)</td>
</tr>
</tbody>
</table>

**Glucose kinetics during extended fasting**

Figure 1 shows the plasma glucose concentration between 8 and 16 hours of fasting. Plasma glucose concentration decreased significantly over time in both groups: severe group from 5.1 (3.5 -- 7.6) to 4.5 (3.0 -- 6.6) mmol/L, non-severe group from 5.0 (4.0 -- 6.1) to 4.4 (2.6 -- 5.5) mmol/L (p < 0.001). The decrease was faster in the non-severe group (18%) than in the severe group (13%) (p = 0.029).

Figure 2 shows endogenous glucose production between 8 and 16 hours of fasting. EGP decreased significantly over time in both groups: severe group from 35.9 (27.1 -- 49.9) to 32.9 (22.6 -- 41.6) µmol/kg•min, non-severe group from 37.4 (29.3 -- 47.0) to 30.9 (20.9 -- 44.3) µmol/kg•min (p < 0.001). There were no differences between the groups (p = 0.954). Gluconeogenesis did not change over time in either group: severe group from 21.3 (10.7 -- 34.8) to 19.1 (10.5 -- 35.1) µmol/kg•min, non-severe group from 20.6 (8.0 -- 33.0) to 20.4 (8.7 -- 35.5) µmol/kg•min (p = 0.151 for change over time, p = 0.841 for difference between groups).

The contribution of gluconeogenesis to endogenous glucose production increased in both groups between 8 and 16 hours of fasting: from 59% to 61% in the severe and from 59% to 65% in the non-severe group (p < 0.001 for change over time, no difference between groups, p = 0.963).

Age and nutritional status did not influence glucose kinetics over time: for plasma glucose concentration: p = 0.244 and p = 0.987 respectively, for EGP: p = 0.271 and p = 0.954 and for gluconeogenesis: p = 0.454 and p = 0.841.
Hormones, the gluconeogenic precursor alanine, and FFA

Data are shown in table 3. During the period of extended fasting plasma insulin concentrations declined and plasma FFA concentrations increased in both groups. After 8 hours of fasting plasma cortisol concentrations were higher in the severe malaria children, between 8 and 16 hours of fasting cortisol concentrations increased only in the non-severe malaria children. At the end of the study there were no differences in plasma concentrations of glucoregulatory hormones, precursors or free fatty acids between the groups.
**Figure 3.** Endogenous glucose production between 8 and 16 hours of controlled fasting in children with severe and non-severe falciparum malaria. Regression equation severe group: endogenous glucose production = 36.6374 – (0.5589 × time); non-severe group: endogenous glucose production = 37.0693 – (0.5574 × time). Data are means ± SEM.

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

<table>
<thead>
<tr>
<th></th>
<th>severe (n = 12)</th>
<th>non-severe (n = 16)</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>22 (15--109)</td>
<td>15 (15--97)</td>
</tr>
<tr>
<td>Glucagon (ng/L)</td>
<td>87 (48--281)</td>
<td>90 (47--239)</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>870 (310--1670)</td>
<td>980 (145--1180)</td>
</tr>
<tr>
<td>Epinephrine (nmol/L)</td>
<td>0.21 (0.08--0.64)</td>
<td>0.35 (0.10--0.87)</td>
</tr>
<tr>
<td>Norepinephrine (nmol/L)</td>
<td>0.72 (0.10--3.90)</td>
<td>0.54 (0.10--5.54)</td>
</tr>
<tr>
<td>FFA (mmol/L)</td>
<td>0.89 (0.42--1.21)</td>
<td>1.04 (0.57--1.73)</td>
</tr>
</tbody>
</table>

DISCUSSION

This is the first study on glucose kinetics in children under the age of five with falciparum malaria during a 16 hour period of controlled fasting. Fasting proved to be an important risk factor for hypoglycemia in young children with severe and non-severe malaria. Contrary to the general opinion, severe malaria did not induce hypoglycemia, but the decline in glucose concentration was slower in children with severe malaria than in non-severe malaria. This means that hypoglycemia due to prolonged fasting would develop...
later in severe than in non-severe malaria. Age and nutritional status were no major
determinants of glucose kinetics in the children during this study.
Plasma glucose concentrations were comparable in the severe malaria and non-severe
malaria children after 8 hours of controlled fasting. During the following 8 hours of
controlled fasting plasma glucose concentrations decreased in both groups, but the
decrease was faster in the non-severe group. With the assumption that the decrease
of plasma glucose concentration would be linear in time in both groups we calculated
the period after which hypoglycemia (mean plasma glucose < 3.0 mmol/l) would occur.
Linear regression analysis, using a mixed linear model, showed that the non-severe
malaria children would develop hypoglycemia after 26 hours of controlled fasting and
the severe malaria children after 33 hours (p = 0.036). The fasting duration prior to the
study must also be taken into account. However, this information can only be obtained
from the patient history, and can not be confirmed objectively. In this study the fasting
duration prior to the study was around 12 hours in both groups. Adding this fasting
duration, non-severe malaria children would become hypoglycemic after 38 hours and
children with severe malaria after 45 hours.
The influence of severity of infection is consistent with the observation that hyperglycemia
rather than hypoglycemia is frequently found in sepsis and other acute infections, as
well as in earlier studies of subjects with falciparum malaria. Since the plasma glucose
concentration decreased less rapidly in the more severely infected children it apparently is
not malaria in itself that causes hypoglycemia.
There are no studies on glucose kinetics in children under the age of five during controlled
extended fasting to compare our results with. Since healthy prepubertal children are
not able to maintain a normal plasma glucose concentration after a fasting period of
24 hours, younger healthy children may develop hypoglycemia after even a shorter
period of fasting. From this study we extrapolated that children with malaria can maintain
a normal plasma glucose concentration for at least 26 hours of fasting.
There were some differences in clinical and biochemical parameters between the
groups of severe malaria and non-severe malaria children that could be of influence on
the decline in plasma glucose concentration. The severe malaria children had a longer
duration of illness although this did not result in a faster decline of the plasma glucose
concentration or endogenous glucose production than in the non-severe malaria children.
The other differences between the groups were all consistent with severe disease. This
also concerns nutritional status: although there were no differences between the groups,
three of the severe malaria children and one of the non-severe malaria children had a
weight-for-height < -2 SD and could be considered malnourished. This partly will have
been due to alteration of the initial nutritional status because of longer duration of illness
and more severe disease leading to acute malnutrition in some of the severe malaria
children. Nevertheless, nutritional status did not influence plasma glucose concentration
during the extended fasting period. The single determining factor for the decrease in
plasma glucose concentration in both severe malaria and non-severe malaria children
proved to be the time of controlled fasting during the study. We conclude that the most important determinant for hypoglycemia in young children with severe and non-severe malaria is the fasting duration.

The plasma glucose concentration is the resultant of the balance between glucose supply and glucose utilization. Hypoglycemia can be caused by diminished glucose production, an increase of glucose clearance, or a combination of both. Endogenous glucose production decreased in both groups during fasting, but there was no difference between the non-severe and the severe group. Since plasma glucose concentration decreased faster in the non-severe malaria children it means that glucose clearance was lower in the severe malaria children. This indicates that malaria, like other inflammatory diseases, results in decreased glucose clearance in these children, a phenomenon that is well known during acute infections in humans.\(^{35}\)

Absolute gluconeogenesis did not change over time in either group. However, as endogenous glucose production decreased, the fractional gluconeogenesis (contribution of gluconeogenesis to glucose production) increased in both groups. When compared to other groups of patients with malaria, fractional gluconeogenesis in these children was low: the fractional gluconeogenesis after 20 hours of fasting in adults with cerebral malaria was 100\%,\(^{14}\) in adults with non-severe malaria 90\%.\(^{13}\) in pregnant women with falciparum malaria 74\% \(^{8}\) and in Kenyan children aged 2 -- 6.5 years with non-severe malaria 74\% after 8 hours of fasting.\(^{23}\) However, this also implies that glycogenolysis still contributed 35--40\% to glucose production after 16 hours of fasting in the children we studied. This is remarkable since glycogen stores in the infant and young child are supposed to be only adequate for a fasting period of 12 hours.\(^{36}\) There are no other studies measuring liver glycogen content in children under five years of age. There are also no data on glucose production and gluconeogenesis in healthy children or in children with malaria or other comparable illnesses under the age of five during prolonged fasting to compare our results.

In conclusion: fasting predisposes for hypoglycemia in young children with severe and non-severe falciparum malaria. Hypoglycemia due to fasting develops later in young children with severe malaria than in children with non-severe malaria. This is most likely due to a difference in peripheral uptake of glucose, indicating that children with severe malaria are more insulin resistant than children with non-severe malaria.

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