Glucose Metabolism in Severe Malaria: Minimal Model Analysis of the Intravenous Glucose Tolerance Test Incorporating a Stable Glucose Label

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Basal plasma glucose is usually increased in uncomplicated malaria, implying insulin resistance. If the infection progresses, the risk of hypoglycemia will increase as host glucose production becomes insufficient for host/parasite demand. To assess the relative contribution of insulin-mediated and non–insulin-mediated glucose disposal to plasma glucose levels in severe malaria, we studied six healthy controls (two males and four females; mean age, 38 years) and eight patients with complicated falciparum malaria (five males and three females; mean age, 31 years) who had a frequently sampled intravenous glucose tolerance test (FSIVGTT) in which 10% of the dextrose bolus was 6,6-D_2-glucose. The minimal model was applied to native and labeled plasma glucose and serum insulin profiles over 4 hours postinjection. Basal plasma glucose concentrations in the patients were significantly greater than in the controls (median [range], 6.1 [2.1 to 8.5] *v* 4.3 [3.9 to 4.7] mmol/L, $P = .03$). Malaria-associated insulin resistance was confirmed by a lower insulin sensitivity index (SI) in patients (5.6 [2.4 to 17.4] *v* 16.0 [2.5 to 22.3] $\times 10^{-4} \cdot min^{-1}$ per μU/mL in controls, $P = .026$). Glucose effectiveness ([SG] the ability of glucose to reduce its own plasma concentration) was higher in the patients (0.015 [0.006 to 0.024] *v* 0.008 [0.007 to 0.010] min^{-1} in controls, $P = .019$). Glucose disappearance at basal concentration was increased by a median of 42% in severe malaria patients, with the insulin-independent component comprising 81%, versus 67% in controls. Indices of β-cell function were normal in malaria patients. These data demonstrate that basal plasma glucose utilization is increased approximately 50% in severe malaria, consistent with previously published isotope-turnover studies. Altered SG plays a major role. Prevention and treatment of early hypoglycemia should be based on adequate glucose replacement. Strategies that reduce insulin secretion or effects appear to be of minor importance.

HYPOGLYCEMIA occurs commonly in severe falciparum malaria.[1] Recent data from large-scale treatment trials suggest that approximately one in 10 adult patients [2] and one in five children[3] will present with this complication, and that a greater proportion become hypoglycemic during treatment. Hypoglycemia results from a variety of processes. There is evidence that reduced tissue insulin sensitivity may increase basal plasma glucose in severe malaria[4] and thus be protective. However, pretreatment glucose turnover is accelerated approximately 50% above normal.[5] Taken together, these findings imply that non–insulin-mediated glucose disposal is increased, contributing to hypoglycemia in severely ill patients whose hepatic glucose production cannot be maintained commensurate with requirements.

However, the role of insulin should not be ignored. Increased basal serum insulin, an appropriate response to tissue insulin insensitivity, can be further augmented by quinine treatment. Quinine remains an effective drug for treatment of severe falciparum malaria,[2,3] but its stimulatory effect on pancreatic β cells[6,7] increases the proportion of severely ill adults experiencing hypoglycemia during treatment to one in four.[2] Nevertheless, initial quinine administration paradoxically reduces glucose turnover,[5] perhaps through effects on the obligatory glucose metabolism of *Plasmodium falciparum,* or even on non–insulin-mediated glucose disposal in the infected host, before hyperinsulinemia due to increasing plasma quinine becomes the overriding influence.

To investigate the relative contribution of non–insulin-mediated and insulin-mediated glucose disposal and quinine treatment to plasma glucose levels in severe malaria, we used the stable-label frequently sampled intravenous glucose tolerance test (FSIVGTT) and minimal model analysis[8,9] in patients with well-characterized, complicated *P falciparum* infection and healthy control subjects. The results parallel those of previous isotopic turnover studies, indicating that glucose disposal at basal concentration is approximately 50% increased in severe malaria. This increase is due to greater non–insulin-mediated glucose disappearance.

SUBJECTS AND METHODS

Subjects

Eight nonpregnant Vietnamese adults with severe falciparum malaria[1] and six healthy volunteers were recruited (Table 1). The patients had been admitted to Cho Ray Hospital, Ho Chi Minh City, for intensive care after an inadequate response to initial treatment in a district hospital. The control subjects were hospital workers or relatives or friends of the patients who were afebrile, slide-negative for malaria, and taking no regular medication at the time of study. All 14 subjects were lean (body mass index <21.0 kg/m^2), and none had preexisting chronic illness, including diabetes. Each subject, or in the case of those in a coma, a first-degree relative, provided witnessed informed consent to the study procedures, which were approved by the Ministry of Health, Vietnam.

Four of eight patients had cerebral malaria with a Glasgow Coma Scale score less than 9 when studied. Of these, two were jaundiced (serum bilirubin >50 μmol/L and serum aspartate transaminase [AST] > twice the upper limit of the control range), one had renal failure that required dialysis, and one had both jaundice and renal failure. Of the remaining four patients, one had renal failure as a sole complication,

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Table 1. Characteristics of the Control Subjects and Patients at Study Entry

Characteristic	Controls (n = 6) Median	Range	Severe Malaria Patients (n = 8) Median	Range
Age (yr)	39	20-58	27	14-58
Sex (male/female)	2/4		5/3	
Body weight (kg)	51	48-55	45	30-53
Oral temperature (°C)	<37.0		37.4	36.5-39.5
Glasgow Coma Scale score	15		9	5-15
Venous hematocrit (%)	38.5	32-42	22.5†	13-31
Parasite density (per μL)	0		4,950	0-304,760‡
Serum creatinine (μmol/L)	86	54-109	93	80-631
Serum bilirubin (μmol/L)	4	1-7	28*	6-156
Serum AST (U/L)	32	7-39	136†	49-266

*$P < .01$.

†$P < .001$.

‡Admitted with 73 parasites/μL, but negative when studied at 12 hours.

one was jaundiced, one had both renal failure and severe anemia (hematocrit <15%), and one had severe anemia alone. Four patients were receiving quinine treatment and four artesunate when studied.

Methods

After an initial clinical assessment and routine laboratory tests, patients were resuscitated and rehydrated with non–dextrose-containing intravenous fluids. Parenteral antimalarial therapy with either quinine or artesunate and monitoring and management of complications were instituted.[1] Each patient was weighed. Regular bedside blood glucose measurements (Exactech; Medisense, Abingdon, UK) were started so that individuals with hypoglycemia (plasma glucose <3.0 mmol/L) could be identified, treated, and excluded from the study. Once each patient's clinical condition was stable, and provided that the patient had been fasting for at least 4 hours, a sampling cannula was inserted into an antecubital vein on the arm opposite that being used for administration of fluids. In the case of patients receiving intravenous quinine, the study was conducted in the 4-hour period between 4-hour infusions given three times daily.

To minimize the volume of blood taken, a modified FSIVGTT[10] was performed in each subject using a standard protocol. Immediately after the basal (0-minute) sample for plasma glucose and serum insulin and quinine was drawn, a sterile injection of dextrose 250 mg/kg body weight was administered over 2 minutes. The dextrose contained 90% unlabeled glucose as a 50% (wt/vol) solution and 10% as a 25-mg/mL solution of 6,6-D_2-glucose (Tracer Technologies, Somerville, MA). Further blood samples were taken at 4, 6, 8, 10, 12, 17, 42, 69, 90, 180, and 240 minutes. Bedside blood glucose measurements were performed at these times and at any other time if the patient developed clinical features of hypoglycemia.

Venous samples for plasma glucose and serum insulin assay were kept on ice and centrifuged promptly at 4°C. Separated plasma and serum were stored at less than −20°C and transported on dry ice before assay. Plasma glucose estimations were performed using the hexokinase method on a Cobas Mira analyzer (Roche, Sydney, Australia). The interassay coefficient of variation was 2.8% at 4.7 mmol/L and 3.5% at 16.6 mmol/L. Serum insulin concentrations were determined by a two-site immunoenzymometric assay (Tosoh, Tokyo, Japan), with a coefficient of variation of 14%, 8%, and 7% at 3.7, 17, and 39 mU/L, respectively. Serum total and unbound quinine concentrations were measured on the 0-minute sample in all patients using high-performance liquid chromatography.[11]

Measurement of 6,6-D_2-glucose levels in plasma was made by gas chromatography/mass spectrometry as described previously.[12,13] In brief, 20 to 50 μL plasma was deproteinized by addition of 1.0 mL absolute ethanol (BDH, Dorset, UK). Following centrifugation, the supernatant was recovered, transferred to a glass derivatization tube, and dried under oxygen-free nitrogen at 50°C. After addition of 100 μL freshly prepared butylboronic acid in pyridine (10 mg/mL; Sigma, St Louis, MO), the samples were derivatized at 95°C for 30 minutes, allowed to cool to room temperature, and mixed with 100 μL acetic anhydride (BDH). The mixture was incubated for 1 hour. The sample was dried under oxygen-free nitrogen at 40°C and resuspended in 200 to 500 μL decane (Sigma). Derivatized samples were analyzed on a Hewlett Packard (Palo Alto, CA) 6170 gas chromatograph/mass spectrometer using a HP1 nonpolar capillary column with selected ion monitoring of M/Z 297/299 at 200°C and a head pressure of helium of 8 psi. Samples from individual infusions were analyzed in batches with an interassay coefficient of variation of 7.4%.

Mathematical Analysis of Plasma Glucose and Serum Insulin

β-Cell function (%B) and insulin sensitivity (%S) were estimated from fasting plasma glucose and serum insulin concentrations using homeostasis model assessment (HOMA[14]). Analysis of the labeled FSIVGTT data was based on the minimal model describing glucose and insulin kinetics[8,15,16]:

$$G^1 = -(p1 + X)\,G + Gin \quad (1)$$

$$\text{and } X^1 = -p2X + p3(I - Ib), \quad (2)$$

where

$$G(0) = 0 \quad \text{and} \quad X(0) = 0,$$

G is the plasma tracer concentration (mg/dL); I, plasma insulin concentration (mU/L); Gin, pulsed application of labeled glucose (mg/min); X, insulin response in the remote compartment (min^{-1}); Ib, basal plasma insulin (mU/L); p1, rate constant for glucose-mediated glucose removal (min^{-1}); p2, rate constant for insulin elimination from the remote insulin compartment (min^{-1}); and p3, rate at which the insulin above basal is delivered to the remote site ($min^{-1} \cdot mU^{-1} \cdot L$).

Equations 1 and 2 were represented in SAAM syntax and solved using CONSAM software.[17] Specifically, G′ and X′ were represented using ordinary-state variables (G, nonlinear; X, linear), and I was represented using a segmented (or piecewise) linear system automatically constructed in SAAM in conjunction with application of the "QL" operational unit to serum insulin data. The subsequent equations were solved using the Chu-Berman numerical integrator,[18] the default and preferred scheme in SAAM for nonlinear systems of differential equations.

To incorporate the tracee glucose into the analysis, an additional state equation was derived from equation 1 by simply adding a constant term, p1 · p4, where p4 = Gb · V1 represents the hepatic glucose production rate at steady state and V1 is the assumed volume of distribution.[19] In all, there were three state equations and one segmented linear function represented in SAAM syntax to model the four components. The parameters p1, p2, p3, and p4 were estimated using the Marquardt-style[20] nonlinear estimation procedure in CONSAM. Initial estimates for p1, p2, and p3 were obtained as described previously.[15] To assign uncertainty to the data in conjunction with data-fitting, a constant fractional standard deviation weighting scheme was used.[21] The fitting objective was the weighted squared deviation.

The insulin sensitivity index (SI) was calculated as the ratio p3/p2 and expressed in units times 10^{-4} per minute per microunit per milliliter. Glucose effectiveness (SG), or the ability of glucose to influence its own disposal, was taken as the rate constant p1 in $minutes^{-1}$. Total glucose disappearance at basal glucose was the sum of insulin-dependent (SI · Ib) and non–insulin-dependent (SG) components. The acute insulin response to glucose ($AIR_{glucose}$) was the mean increase in serum insulin above basal in samples taken during the first 10 minutes after dextrose injection.

Statistical Analysis

Because the number of patients and controls was small, and several variables did not conform to a normal distribution (including serum insulin, %B, and %S), nonparametric tests (SPSS for Windows; SPSS, Chicago, IL) were used in the analysis, and data are reported as the median and range unless otherwise stated. Two-sample comparisons were made using the Wilcoxon-Mann-Whitney test, and the Spearman rank correlation coefficient was used to assess associations between variables.

RESULTS

Clinical Course

Six patients responded to treatment and were discharged aparasitemic and afebrile after a median of 13 days (range, 8 to 16) in hospital. The median parasite clearance time was 61 hours (range, 13 to 115). Two patients died in hospital. The first was a 20-year-old male who had cerebral malaria, renal failure requiring peritoneal dialysis, gastrointestinal hemorrhage, metabolic acidosis, and shock that was refractory to inotropic support. He died during the second day of intensive treatment. The second was a 28-year-old male with cerebral malaria, renal failure necessitating dialysis, and jaundice who also died of cardiorespiratory failure 6 days after starting treatment. Both were treated with quinine, and on the first and third day, respectively, after undergoing FSIVGTT, they developed hypoglycemia that responded to parenteral dextrose replacement.

Basal Plasma Glucose and Serum Insulin

Patients with severe malaria had significantly higher basal plasma glucose than the controls (median [range], 6.1 [2.1 to 8.5] *v* 4.3 [3.9 to 4.7] mmol/L, $P = .03$; Table 2). There was a similar trend in serum insulin, which did not achieve statistical significance (4.9 [2.0 to 17.1] *v* 3.0 [2.0 to 6.3] mU/L, $P = .06$). However, one patient (the 20-year-old who died within 48 hours of admission) was found to be hypoglycemic (plasma glucose, 2.1 mmol/L) on subsequent hexokinase assay despite a bedside blood glucose greater than 3.0 mmol/L pre-FSIVGTT. This patient had a correspondingly low serum insulin (2.0 mU/L). When this patient was excluded from the analysis, both plasma glucose and serum insulin were significantly higher in patients than in controls ($P \leq .03$; Table 2). In terms of the HOMA model, nonhypoglycemic patients had significantly reduced %S ($P = .01$), but values for %B were not significantly different from those in the control subjects ($P = .22$; Table 2).

Serum Quinine

Serum quinine assay on basal samples showed free levels greater than 0.1 mg/L in five patients. One artesunate-treated patient had total and free serum quinine concentrations indicating that quinine therapy had been given before admission to Cho Ray Hospital. The median [range] for total and free serum quinine was 5.7 [1.6 to 11.2] and 0.5 [0.2 to 0.6] mg/L, respectively.

Table 2. Basal Plasma Glucose, Serum Insulin, and HOMA-Derived %B and %S

	Controls (n = 6)		Severe Malaria Patients (n = 7)	
Parameter	Median	Range	Median	Range
Plasma glucose (mmol/L)	4.3	3.9-4.7	6.1*	4.0-8.5
Serum insulin (mU/L)	3.0	2.0-6.3	4.9*	3.2-17.1
%B	89	73-137	64	23-214
%S	136	64-207	66*	21-102

NOTE. One hypoglycemic patient was excluded from analysis.
*$P < .05$.

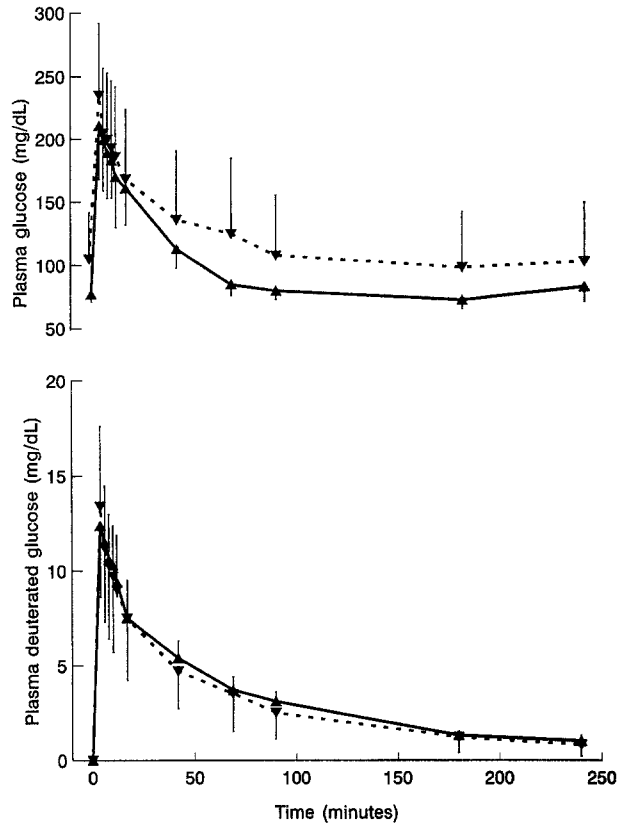

Fig 1. Plasma glucose and 6,6-D_2-glucose concentrations in control subjects (▲) and patients with severe malaria (▼) before and after injection of dextrose 250 mg/kg body weight, of which 10% was 6,6-D_2-glucose. Data are the mean ± SD.

Stable-Label Minimal Model Data

Plasma glucose, plasma 6,6-D_2-glucose, and serum insulin profiles in both groups of subjects are shown in Figs 1 and 2. Derived minimal model and other parameters are summarized in Table 3. Patients with severe malaria had significantly lower SI values than the controls ($P = .026$), but SG was significantly increased in the severe malaria group ($P = .019$; Fig 3). The net effect of these changes on basal glucose disappearance was a median increase of approximately 42% in malaria patients, most of which was accounted for by non–insulin-mediated glucose disposal (Table 3 and Fig 4). There was no significant difference between $AIR_{glucose}$ values in patients and controls (Table 3).

There was an inverse correlation between SI and simultaneous parasitemia in the severe malaria group ($r_s = -.74$, $P = .018$), but no other significant associations between either SI or SG and baseline parasite count or biochemical variables including indices of hepatic and renal function. The patient found to be hypoglycemic at the time of study had the highest SI and SG of the eight patients (Fig 3) and the highest basal plasma glucose disposal rate of any subject studied. The other fatal case who became hypoglycemic did so several days after the

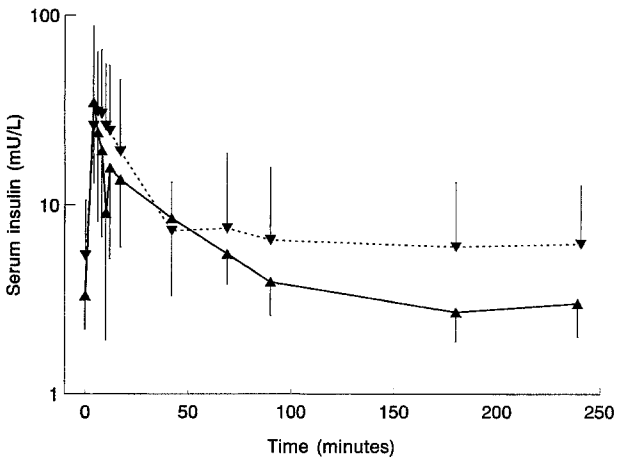

Fig 2. Serum insulin concentrations in control subjects (▲) and patients with severe malaria (▼) before and after injection of dextrose 250 mg/kg. Data are the geometric mean ± SD.

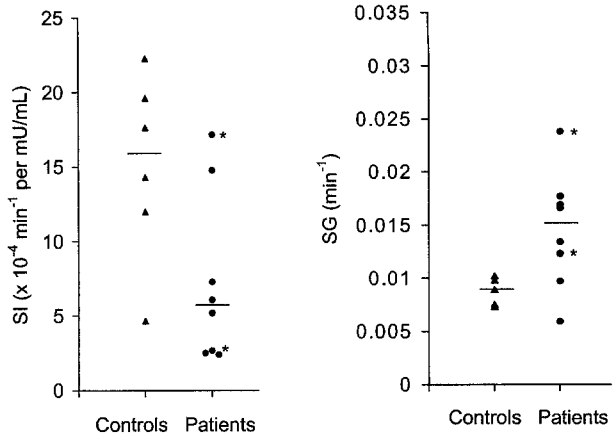

Fig 3. Measures of SI and SG in control subjects and patients with severe malaria from minimal model analysis of stable-label FSIVGTT data. Group medians are indicated by horizontal bars. *Patients who died in hospital.

FSIVGTT. At the time of study, this latter patient had a low SI and a SG close to the group median (Fig 3).

Quinine Effects on Glucose Metabolism

Five patients with a measurable serum quinine level had a significantly lower plasma glucose than the three patients with an undetectable quinine concentration at baseline ($P = .03$; Table 4). Basal serum insulin tended to be higher ($P = .09$), especially when the suppressed serum insulin concentration in the quinine-treated hypoglycemic patient was excluded ($P = .01$; Table 4). The total rate of glucose disappearance at basal concentrations and that attributable to insulin were also higher in quinine-treated patients ($P \leq .05$; Table 4 and Fig 4). Glucose disappearance due to non–insulin-mediated disposal was similar in quinine-treated and untreated patients ($P = .12$), as were other minimal model parameters including SG and SI ($P > .1$; Fig 4).

DISCUSSION

Severe falciparum malaria can be considered a multisystem disease. Endocrine dysfunction and metabolic disturbances are both common and potentially life-threatening, and hypoglycemia is the most frequently encountered metabolic complication.[22] Our results indicate that, consistent with radioisotopic-turnover studies in a comparable group of patients with severe malaria,[5] glucose demand is increased approximately 50%. In addition, insulin-dependent glucose disposal is reduced in relative and absolute terms. Quinine treatment increases the insulin-dependent component through β-cell stimulation, but only to a level equivalent to that of normal subjects. These findings provide new data relating to the pathogenesis of hypoglycemia in patients with severe falciparum malaria, and may also assist in designing measures to both prevent and reverse this complication.

Although comprising a small sample, our patients had a range of complications and mortality (25%) that were typical of those found in larger series of patients with severe malaria managed in Vietnamese hospitals.[2,23] They presented with generally elevated basal plasma glucose and serum insulin indicative of tissue insulin insensitivity, which was confirmed on HOMA analysis. In addition, minimal model analysis of stable-label FSIVGTT data from our patients generated SI values that were significantly less than those of the controls. This finding is consistent with previous estimates of SI in Thai patients with severe malaria,[4] even though the analysis was made on only

Table 3. Measures Derived From Minimal Model Analysis of the Labeled FSIVGTT

	Controls (n = 6)		Severe Malaria Patients (n = 8)	
Measure	Median	Range	Median	Range
SI ($10^{-4} \cdot min^{-1}$ per μU/mL)	16.0	4.5-22.3	5.6*	2.4-17.2
SG (min^{-1})	0.0082	0.0073-0.0102	0.0150*	0.0059-0.0238
Total glucose disappearance at basal glucose (min^{-1})	0.012	0.009-0.014	0.017†	0.013-0.027
Insulin-independent glucose disappearance (% of total)	67	55-75	81†	37-96
$AIR_{glucose}$ (mU/L)	15.1	8.8-139.2	28.5	5.9-52.1

*$P < .05$.
†$P < .01$.

Table 4. Measures Derived From Minimal Model Analysis of the Labeled FSIVGTT in Patients With and Without Detectable Serum Quinine Concentrations

	No Quinine (n = 3)		Quinine (n = 5)	
Measure	Median	Range	Median	Range
Plasma glucose	7.8	6.1-8.5	5.1*	2.1-6.7
Serum insulin	4.1	3.2-4.2	6.9	2.0-17.1
Total glucose disappearance at basal glucose (min^{-1})	0.016	0.013-0.018	0.018*	0.016-0.027
Insulin-independent glucose disappearance (% of total)	84	76-96	77	37-92
$AIR_{glucose}$ (mU/L)	35.1	6.6-40.5	21.9	5.9-52.1

*$P < .05$.

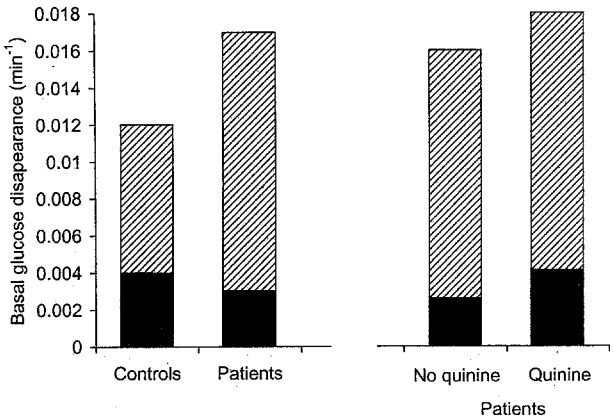

Fig 4. Glucose disappearance rate at basal plasma glucose estimated using the minimal model in controls and patients with severe malaria (left) and in the patients subdivided by treatment type (right). Data represent group medians for non–insulin-mediated glucose disposal (▨) and insulin-mediated glucose disposal (■) in each case.

three severely ill patients, the dose of unlabeled dextrose and the sampling schedule were nonstandard, and control data from the published literature were used for comparison.[4]

Measures of SI in our patients and controls were generally higher than previously reported for both healthy controls (a mean of $7.6 \times 10^{-4} \cdot min^{-1}$ per μU/mL in young male caucasians[10]) and the small sample of Thai patients with severe malaria ($2.9 \times 10^{-4} \cdot min^{-1}$ per μU/mL[4]). Nevertheless, our subjects were lean farmers or rural laborers, with the controls having a mean body mass index of 19.1 kg/m^2 and the patients 18.2 kg/m^2. This may have served to elevate SI, especially in the case of the controls. In addition, the use of a stable label as part of the FSIVGTT is known to increase minimal model estimates of SI compared with the use of unlabeled dextrose alone.[9] In any case, we were interested primarily in the comparison between patients and controls using identical methodology.

Estimates of SG vary less than those of SI, with reported means typically within the range of 0.020 to 0.025 min^{-1}.[24] Values for SG in our controls were below this range, but analogous to minimal model analysis of SI, the use of a stable label produces lower estimates of SG compared with the use of unlabeled dextrose.[9] In addition, subjects such as ours who are on a very–low-calorie diet also tend to have a low SG.[25] Physiological increases in SG on the order of those found in our severely ill patients are restricted to acute exercise and result from physical training,[26,27] but this has not been a consistent finding.[28]

Increases in SG in severe malaria could relate to the effects of stress or the infection per se on expression of cellular glucose transporters (GLUT). Non–insulin-mediated glucose disposal has also been shown to increase in bacterial infection in animals,[29] and both thermal injury and sepsis increase expression of GLUT-1 in macrophages and the brain in animal models.[30,31] Tumor necrosis factor-alpha (TNF-α) and bacterial lipopolysaccharide (LPS) may have a role in this change.[32] It is possible that in patients with malaria who have generally increased circulating levels of TNF-α[33] and in whom LPS-like parasite products may be present, a similar effect on GLUT-1 expression occurs that acts to increase SG. The *P falciparum* parasite itself may also metabolize glucose and contribute to the increased estimates of SG in our patients. Nevertheless, peripheral parasitemia was generally low, and antimalarial treatment had already been given at the time of study. Even if there were a comparable number of more mature and metabolically active parasite forms sequestered in the microvasculature,[34] it is unlikely that the total parasite biomass would produce the observed changes in SG. The inverse relationship between parasitemia and SI suggests that patients with the greatest parasite burden are also the most insulin-resistant, which would partially counteract any effect of parasite glucose metabolism.

Estimates of glucose uptake in normal subjects at basal plasma glucose suggest that approximately 60% is due to SG,[24] a figure close to the 67% for non–insulin-dependent glucose disposal found in our controls. The effect of malaria is to increase this proportion to an average of greater than 80%. In absolute terms, SG is doubled in severe malaria while, because of an increase in SI, insulin-mediated glucose disposal decreases (Fig 4). This finding underlines the importance of adequate dextrose replacement in the prevention and treatment of early hypoglycemia. Strategies to attenuate insulin secretion or effectiveness (such as administration of a somatostatin analog[35] and infusion of lipid emulsion[36]) would appear to be of relatively minor importance, at least during the initial stages of treatment; this includes patients receiving quinine. Although the component of basal glucose disappearance mediated by insulin in this subgroup was greater than in artesunate-treated patients and comparable to that in controls (Fig 4), non–insulin-mediated glucose disposal was still double that in our healthy subjects.

However, the effect of quinine on insulin secretion may become more important later in the clinical course of patients treated with this drug when plasma quinine concentrations are maximal, especially in those with hepatorenal dysfunction. The two patients who died of cardiorespiratory failure had multiple organ dysfunction and were both treated with quinine. They were the only patients who developed hypoglycemia, and it was most marked after 24 hours of quinine therapy. Interventions that reduce β-cell function or induce insulin resistance might have been appropriate in these patients at this time.

The results of minimal model analysis of stable-label FSIVGTT data in the present study confirm available preliminary evidence that severe malaria reduces insulin sensitivity as assessed by measurement of SI. However, the net effect of this change on basal plasma glucose disposal is relatively small compared with the simultaneous increase in SG. Severe malaria is one of a small number of physiological or pathophysiological states in which increased SG has been observed, and infection-associated increases in GLUT-1 expression may be at least partially responsible. Further studies are needed to examine the relationship between glucose kinetics, GLUT expression, and the cytokine milieu in patients with severe falciparum malaria.

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REFERENCES

1. Warrell DA, Molyneux M, Beales P: Severe and complicated malaria. Trans R Soc Trop Med Hyg 84:1-69, 1990 (suppl 2)

2. Tran TH, Day NP, Nguyen HP, et al: A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. N Engl J Med 335:76-83, 1996

3. Van-Hensbroek MB, Onyiorah E, Jaffar S, et al: A trial of artemether or quinine in children with cerebral malaria. N Engl J Med 335:69-75, 1996

4. Pukrittayakamee S, Davis TME, Levy J, et al: The metabolic response to rapid intravenous glucose injection in acute falciparum malaria. Trans R Soc Trop Med Hyg 85:189-193, 1991

5. Davis TME, Looareesuwan S, Pukrittayakamee S, et al: Glucose turnover in severe falciparum malaria. Metabolism 42:334-340, 1993

6. Henquin JC, Horemans B, Nenquin M, et al: Quinine-induced modifications of insulin release and glucose metabolism by isolated pancreatic islets. FEBS Lett 57:280-284, 1975

7. Davis TME, Karbwang J, Looareesuwan S, et al: Comparative effects of quinine and quinidine on glucose metabolism in normal man. B J Clin Pharmacol 30:397-403, 1990

8. Cobelli C, Pacini G, Toffolo G, et al: Estimation of insulin sensitivity and glucose clearance from minimal: New insights from labeled IVGTT. Am J Physiol 250:E591-E597, 1986

9. Avogaro A, Bristow JD, Bier DM, et al: Stable-label intravenous glucose tolerance test minimal model. Diabetes 38:1048-1055, 1989

10. Bergman RN, Ader M: Concepts emerging from the minimal model approach. Curr Top Diabetes Res 12:39-65, 1993

11. Dyer JR, Davis TME, Giele C, et al: The pharmacokinetics and pharmacodynamics of quinine in the diabetic and non-diabetic elderly. Br J Clin Pharmacol 38:205-212, 1994

12. Weicko J, Sherman WR: Boroacetylation of carbohydrates. Correlations between structure and mass spectral behaviour in monoacetylhexose cyclic boronic esters. J Am Chem Soc 98:7631-7637, 1976

13. Davis TME, Suputtamongkol Y, Spencer J, et al: Glucose turnover in pregnant women with acute malaria. Clin Sci 86:83-90, 1994

14. Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412-419, 1985

15. Bergman RN, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man: Measurement of insulin sensitivity and b-cell glucose sensitivity from response to intravenous glucose. J Clin Invest 68:1456-1467, 1981

16. Bowes SB, Hennessy TR, Umpleby AM, et al: Measurement of glucose metabolism and insulin secretion during normal pregnancy complicated by gestational diabetes. Diabetologia 39:976-983, 1996

17. Boston RC, Greif PC, Berman M: Conversational SAAM—An interactive program for the kinetic analysis of biological systems. Comput Programs Biomed 13:111-119, 1981

18. Chu SC, Berman M: An exponential method for the solution of systems of ordinary differential equations. Commun Assoc Comput Machin 17 12:699-702, 1974

19. Brun J-F, Fedou C, Monnier J-F, et al: Relationships between insulin resistance measured with the minimal model and microalbuminuria in type 2 (non–insulin-dependent) diabetics. Endocrinol Metab 2:203-213, 1995

20. Marquardt DW: An algorithm for the estimation of nonlinear parameters. J Soc Indust Appl Math 11:431-441, 1963

21. Caumo A, Giacca A, Morgese M, et al: Minimal models of glucose disappearance: Lessons from the labeled IVGTT. Diabet Med 8:822-832, 1991

22. White NJ, Ho M: The pathophysiology of malaria. Adv Parasitol 31:83-173, 1992

23. St John A, Davis TME, Binh TQ, et al: Mineral homeostasis in acute renal failure complicating severe falciparum malaria. J Clin Endocrinol Metab 80:2761-2767, 1995

24. Best JD, Kahn SE, Ader MA, et al: Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 19:1018-1030, 1996

25. Nakai Y, Taniguchi A, Fukushima M, et al: Insulin sensitivity during very–low-calorie diets assessed by minimal modeling. Am J Clin Nutr 56:179S-181S, 1992 (suppl 1)

26. Brun JF, Guintrand-Hugret R, Boegner C, et al: Influence of short-term submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. Metabolism 44:833-840, 1995

27. Tokuyama K, Higaki Y, Fujitani J, et al: Intravenous glucose tolerance test–derived glucose effectiveness in physically trained humans. Am J Physiol 265:E298-E303, 1993

28. Kahn SE, Larson VG, Schwartz RS, et al: Exercise training delineates the importance of B-cell dysfunction to the glucose intolerance of human aging. J Clin Endocrinol Metab 74:1336-1342, 1992

29. Lang CH, Dobrescu C: Gram-negative infection increases noninsulin-mediated glucose disposal. Endocrinology 128:645-653, 1991

30. Gamelli RL, Liu H, He LK, et al: Alterations of glucose transporter mRNA and protein levels in brain following thermal injury and sepsis in mice. Shock 1:395-400, 1994

31. Widnell CC, Baldwin SA, Davies A, et al: Cellular stress induces a redistribution of the glucose transporter. FASEB J 4:1634-1637, 1990

32. Gamelli RL, Liu H, He LK, et al: Augmentations of glucose uptake and glucose transporter-1 in macrophages following thermal injury and sepsis in mice. J Leukoc Biol 59:639-647, 1996

33. Kern P, Hemmer CJ, Van Damme J, et al: Elevated tumor necrosis factor alpha and interleukin-6 serum levels as markers for complicated *Plasmodium falciparum* malaria. Am J Med 87:139-143, 1989

34. Davis TME, Krishna S, Looareesuwan S, et al: Sequestration and anaemia in severe falciparum malaria: Analysis of changes in venous haematocrit using a simple mathematical model. J Clin Invest 86:793-800, 1990

35. Phillips RE, Looareesuwan S, Molyneux ME, et al: Hypoglycaemia and counterregulatory hormone responses in severe falciparum malaria: Treatment with Sandostatin. Q J Med 86:233-240, 1993

36. Davis TME, Supanaranond W, Pukrittayakamee S, et al: The effect of plasma free fatty acids and long chain triglycerides on glucose metabolism in uncomplicated falciparum malaria. Trans R Soc Trop Med Hyg 89:511-515, 1995