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Serum Apolipoprotein-A1 and Cholesterol Levels in Nigerian Children with *Plasmodium falciparum* Infection

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Key Words
Apolipoprotein-A1 · *Plasmodium falciparum* · Malaria · Lipids

Abstract
Objective: This study was carried out to determine whether or not *Plasmodium falciparum* malaria infection significantly affected apolipoprotein-A1 and cholesterol levels and if apolipoprotein-A1 correlated with the malaria severity in children younger than 5 years old. ***Subjects and Methods:*** Two hundred and fifty-five children, 170 of whom had microscopically confirmed *P. falciparum* infection, i.e. 85 cases of uncomplicated malaria (UM) and 85 of complicated malaria (CM), and 85 healthy controls were enrolled in this study. Serum levels of apolipoprotein-A1, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides were determined. These levels were compared among the malaria and control groups, using ANOVA and post hoc analyses at $p = 0.05$. ***Results:*** There were significant differences in the mean serum levels of apolipoprotein-A1 (UM: 104.5 ± 38.1 mg/dl, CM: 90.9 ± 33.3 mg/dl and controls: 129.7 ± 48.3 mg/dl; $p < 0.001$), total cholesterol (UM: 138.8 ± 62.9 mg/dl, CM: 121.2 ± 55.2 mg/dl and controls: 155.1 ± 69.8 mg/dl; $p = 0.002$) and LDL (UM: 98.2 ± 55.5 mg/dl, CM: 84.3 ± 47.4 mg/dl and controls: 122.7 ± 69.4 mg/dl; $p < 0.001$). Post hoc analyses revealed that children with UM and CM had significantly lower levels of apolipoprotein-A1, cholesterol, HDL and LDL than controls but that there was no difference between the 2 malaria groups. Reductions in levels of lipids and apolipoprotein-A1 were worse in CM than in UM. ***Conclusion:*** Altered levels of serum lipids with CM were associated with a reduction in apolipoprotein-A1. These findings have potential diagnostic utility for the management of malaria.

Introduction

Malaria remains a global health problem and a threat to the life of about 40% of the world population in spite of efforts at prevention and improvements in treatment [1]. Malaria accounts for an estimated 18% of deaths among children younger than 5 years of age worldwide, and >90% of these deaths occur in sub-Saharan Africa [1]. Though the burden of morbidity due to malaria has declined in many countries, the disease and its complications still account for about 30% of childhood mortality, 11% of maternal mortality and 30–40% of out-patient clinic consultations in Nigeria [2].

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Children younger than 5 years are particularly vulnerable to malaria infections and its attendant complications, which can be almost wholly attributed to *Plasmodium falciparum* infection in the sub-Saharan African population [3]. Visser et al. [4] reported on potential biochemical molecules that may be targeted for diagnostic and therapeutic procedures, for example, *P. falciparum*, which thrives by interacting with host molecules like protein and lipids.

Some clinical studies show that the lipid profile of patients with malaria infection changes considerably, to the extent that this could be attributed wholly to the parasitaemia [5, 6]. While some studies report no correlation between the severity of malaria and the extent of lipid profile changes [7, 8], in others, the magnitude of observed changes has been related to the severity of malaria [9, 10]. So far, the existing literature suggests that changes in the lipid profile during malaria illness are transient and occur in the acute phase. Thus, it has been suggested that lipids as well as sub-classes and related metabolites constitute potential adjuvant diagnostic tools for malaria as well as targets for treatment [7, 11, 12].

Apolipoproteins and the sub-class apolipoprotein-A1 are proteins that bind to lipids to form lipoproteins. Their main function is to transport lipids; they play an important role in lipoprotein receptor recognition as well as the regulation of certain enzymes in lipoprotein metabolism [13]. While many studies have reported low lipid levels in patients with malaria [13–15], data in the literature on an inter-relationship between apolipoprotein-A1, cholesterol and *P. falciparum* infection are scarce [15–18]. No meta-analysis has been conducted on the actual effect that malaria has on apolipoprotein because of insufficient data. Notably, a cross-sectional study showed that significantly lowered apolipoprotein-A1 levels occurred in a malaria group but not in healthy individuals [17]. Conversely, Cuisinier-Raynal et al. [18] reported no significant difference in the apolipoprotein-A1 levels of 144 non-immune adults who stayed in Central Africa for 4 months compared to controls. More recently, Simpson et al. [19] demonstrated a lower level of apolipoprotein-A1 in severely anaemic, malaria-exposed primigravidae compared with multigravid pregnant women. Ray et al. [20] suggested the potential discriminatory ability of apolipoprotein-A1 for malaria infection among adults [21]. However, a number of characteristics (the differences between pregnant women/adults and children younger than 5 years) underscore the need to examine the possible peculiarities of lipid metabolism, especially apolipoprotein-A1, in children with malaria.

In Nigeria, two studies [22, 23] found in public domain investigated the influence of malaria infection on cholesterol. The reports of these studies are limited because of the methodology and the number of participants, and neither study assessed the level of apolipoprotein-A1. For instance, Agbedana et al. [23] reported significantly lower levels of serum high-density lipoprotein (HDL) among 15 patients with malaria compared to 15 controls over 24 years ago, but apolipoprotein-A1, a major protein component of HDL, was not measured. More recently, Chukwuocha and Eke [22] investigated the relationship between malaria parasite status and cholesterol level in 110 adults; again, apolipoprotein-A1 was not measured. It is important to note that children were not included in their study and absolute parasite counts were not performed; this makes it difficult to objectively assess the effects of malaria severity on lipids. Thus far, the available literature suggests that children with malaria may exhibit remarkable lipid derangement, but little is known about the serum apolipoprotein-A1 profile during malaria illness. Therefore, this study was carried out to find out whether malaria infection significantly affects apolipoprotein-A1 as well as other lipids in Nigerian children.

Material and Methods

Study Design and Setting

In this case control study, data from 255 children were analyzed and presented. There were 170 cases with microscopically confirmed *P. falciparum* malaria infection, i.e. 85 complicated malaria (CM) and 85 uncomplicated malaria (UM) cases. The controls were 85 healthy children with a negative blood smear for malaria parasites. The cases were age-matched to the controls. The children were grouped according to age: 6–11, 12–23, 24–35, 36–47 and 48–59 months. Cases were recruited from the Children's Clinics and Emergency Unit of the University College Hospital (UCH), Ibadan, Nigeria, from April 2011 to March 2013, while controls were selected from among children living in the same neighbourhood as the respective cases. The UCH is foremost a tertiary referral hospital located in Ibadan, south-west Nigeria. There are approximately 2,500 admissions yearly to the UCH Department of Paediatrics, and about 11% of these are CM cases. Based on the 2006 national census, Ibadan has an estimated population of 2,550,393.

Study Population and Sampling

Ethical approval for the study was obtained from the University of Ibadan/UCH Ibadan Ethics Review Committee. Participation in the study was completely voluntary and based on written informed consent obtained from parents or caregivers, who were made to understand that they were free to refuse consent and that due treatment would not be denied (according to the treatment guideline).

Table 1. Demographic characteristics, weight and parasite counts of children with malaria and controls

	Control (n = 85)	UM (n = 85)	CM (n = 85)	Total (n = 255)
Sex, n (%)				
Male	49 (57.6)	48 (56.5)	59 (56.1)	156 (61.2)
Female	36 (42.4)	37 (43.5)	26 (30.6)	99 (38.8)
Age, months				
Range	6.0–59.0	6.0–56.0	9.0–59.0	6.0–59.0
Median	34.0	32.0	37.0	35.0
Mean ± SD	36.2±10.9	36.3±11.5	32.5±12.3	34.4±11.4
Weight, kg				
Range	6.5–16.0	5.9–15.7	8.5–14.5	5.9–16.0
Median	11.0	10.0	11.5	11.5
Mean ± SD	12.2±3.2	13.4±4.6	14.2±2.3	13.6±4.1
MP counts (per ml)				
Min.–max.	n.a.	446–52,079	1,188–25,7426	n.a.
Median	n.a.	2,376	58317	n.a.
Geometric mean	n.a.	2,259	39,041	n.a.

MP = Malaria parasite; n.a. = not applicable.

All the children were enrolled into the study consecutively, using a non-probability convenient-sampling technique. Children who presented with symptoms and signs suggestive of malaria and a confirmed positive blood smear for malaria parasites were considered as cases. Controls were children of similar socioeconomic status who did not have symptoms of malaria and had a negative blood smear for the malaria parasite. All the children with microscopically confirmed *P. falciparum* malaria infection were febrile (axillary temperature >37.5°C). Cases were grouped into UM and CM as defined by the World Health Organization [3]. All participants were screened for haemoglobinopathy and those with haemoglobin types SS and SC were excluded from the study.

Sample Size Calculation

Before the study, we hypothesised that the lowest mean cholesterol levels would be 130.3 ± 25.2 and 115.9 ± 28.7 mg/dl for healthy controls and cases, respectively. These projections were made from values reported by Agbedana et al. [23]. Using the menu in Stata/SE 12.1 statistical software (StataCorp, College Station, Tex., USA) for estimating sample size for 2-sample comparison at a 95% level of confidence, 90% power and a case-to-control ratio of 2:1, the estimated minimum required sample size for malaria patients was 148 and 74 for controls.

Data Collection

A pre-tested, structured, interviewer-administered questionnaire was used to obtain information from parents/caregivers at the time of recruitment by a trained research assistant. Weight and height were also recorded. Each child was examined by the consultant paediatrician (A.E.O.). Laboratory investigations included a blood smear for malaria parasite counts, haematocrit determination and haemoglobin typing. About 3 ml of blood was collected from each subject and the plasma samples were stored at –20°C until a lipid profile was performed. The malaria parasites were counted against 200 white blood cells, and parasite density was calculated for each patient based on an assumed total white blood cell count of 8,000/μl of blood [24]. All children with malaria received standard treatment according to the national guidelines for the treatment of malaria.

Determination of Lipid Profile

Plasma total cholesterol, HDL and triglyceride levels were determined by an enzymatic colorimetric method using appropriate test kits (Vital Diagnostics SPb Ltd. Petersburg, Russia). The Friedewald formula [25] was used to calculate the low-density lipoprotein (LDL) cholesterol concentration except in participants with serum triglyceride levels >309 mg/dl (<8.0 mmol/l). Apolipoprotein-A1 levels were determined by turbidimetric measurement using test kits (DIALAB Production GmbH, Wiener Neudorf, Austria).

Statistical Analyses

Data were analyzed using the Statistical Package for Social Scientists (SPSS) 17.0 for Windows (SPSS Inc., Chicago, Ill., USA). All continuous variables were checked for normality using the Shapiro-Wilks test to identify those that were non-parametric in distribution. Analysis of variance (ANOVA) or its non-parametric equivalent, the Kruskal-Wallis H test, was used to compare the mean values of the 3 groups, i.e. the UM, CM and control groups. Post hoc, pair-wise comparisons with Bonferroni's adjustments were also done to detect differences between 2 groups. Spearman's rho correlation analysis was used to assess correlations between parasite counts and plasma levels of lipids. $p < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was carried out to evaluate the individual performance of cholesterol and apolipoprotein-A1 levels for predicting CM, and the resulting curves are displayed.

Table 2. Comparisons of lipid levels for the 2 groups with malaria and the control group

Lipid levels, mg/dl	Control (n = 85)	UM (n = 85)	CM (n = 85)	F-statistic	p value
Total cholesterol	155.1±69.8	138.8±62.9	121.2±55.2	6.16	0.002
LDL	122.7±69.4	98.2±55.5	84.3±47.4	9.55	<0.001
HDL	10.0±8.8	7.9±6.8	7.2±6.4	3.29	0.039
Triglycerides	111.7±55.1	102.1±49.3	100.8±48.4	1.14	0.322
Apolipoprotein-A1	129.7±48.3	104.5±38.1	90.9±33.3	20.21	<0.001

Table 3. Pair-wise comparisons of lipid levels for malarial patients and the control group

Lipid levels, mg/dl	Mean difference	95% CI	p value
Total cholesterol			
UM vs. controls	16.4	−39.6 to 6.9	0.274
CM vs. controls	33.9	−57.1 to −10.6	0.002
CM vs. UM	17.5	−40.7 to 5.7	0.212
LDL			
UM vs. controls	24.6	−46.0 to −3.1	0.019
CM vs. controls	38.5	−59.9 to −17.0	<0.001
CM vs. UM	13.9	−35.4 to 7.6	0.359
HDL			
UM vs. controls	2.1	−4.8 to 0.7	0.205
CM vs. controls	2.8	−5.5 to −0.1	0.043
CM vs. UM	0.7	−3.5 to 2.0	1.000
Triglycerides			
UM vs. controls	9.5	−28.4 to 9.3	0.673
CM vs. controls	10.8	−29.6 to 8.1	0.507
CM vs. UM	1.3	−20.1 to 17.6	0.898
Apolipoprotein-A1			
UM vs. controls	25.3	−23.9 to −10.3	<0.001
CM vs. controls	38.8	−53.8 to −23.9	<0.001
CM vs. UM	13.6	−28.5 to 1.4	0.089

Table 4. Correlations of parasite counts and plasma lipid levels in malaria patients by means of Spearman rho correlation analysis

	UM		CM	
	r	p	r	p
Total cholesterol	−0.019	0.865	−0.209	0.055
LDL	0.053	0.633	0.134	0.221
HDL	−0.008	0.944	−0.012	0.914
Triglycerides	0.022	0.839	−0.104	0.342
Apolipoprotein-A1	−0.413	0.003	−0.532	<0.001

Results

Demographics, Clinical Data and Parasite Counts

Demographic characteristics, weight and parasite counts of the children with malaria and the controls are shown in table 1. In all, there were more male than female children (males:females = 1.6:1). The mean age of children with CM (32.5 ± 12.3 months), UM (36.3 ± 11.5 months) and controls (36.2 ± 10.9 months) was not significantly different (F = 2.972, d.f. = 2, 252; p = 0.053). Although age is an important determinant of malaria morbidity, there was no statistical difference in the distribution of UM, CM and control groups with respect to age. There was also no significant difference in the mean weight (in kilograms) of all 3 groups. However, the parasite count (per microlitre) of the children in the CM group (median 58,317 and range 1,188–257,426) was significantly higher than in the UM group (median 2,376 and range 446–52,079).

Of the 85 children in the CM group, 28 (32.9%) presented with severe anaemia (haemoglobin <5 g/dl), 19 (22.4%) had an altered level of consciousness, 17 (20.0%) had a history of passing dark urine plus positive urine dipstick test results for blood, 9 (10.6%) had respiratory distress plus acidosis, 8 (9.40%) had multiple convulsions and 7 had (8.2%) prostration. Two children presented with oliguria (i.e. a urine output <1.0 ml/m^2/h) which resolved within 48 h of admission following the administration of intravenous fluid. All of the 28 children with severe anaemia were transfused with packed red blood cells at 10–15 ml/kg of body weight. None of the study patients had any established signs of shock and no deaths occurred.

Lipid Profile of the Study Participants

The mean values of the serum lipids for the 3 groups are shown in table 2. All plasma lipids except for triglycerides were significantly lower in the malaria groups (UM and CM) than in the controls. Post hoc analyses

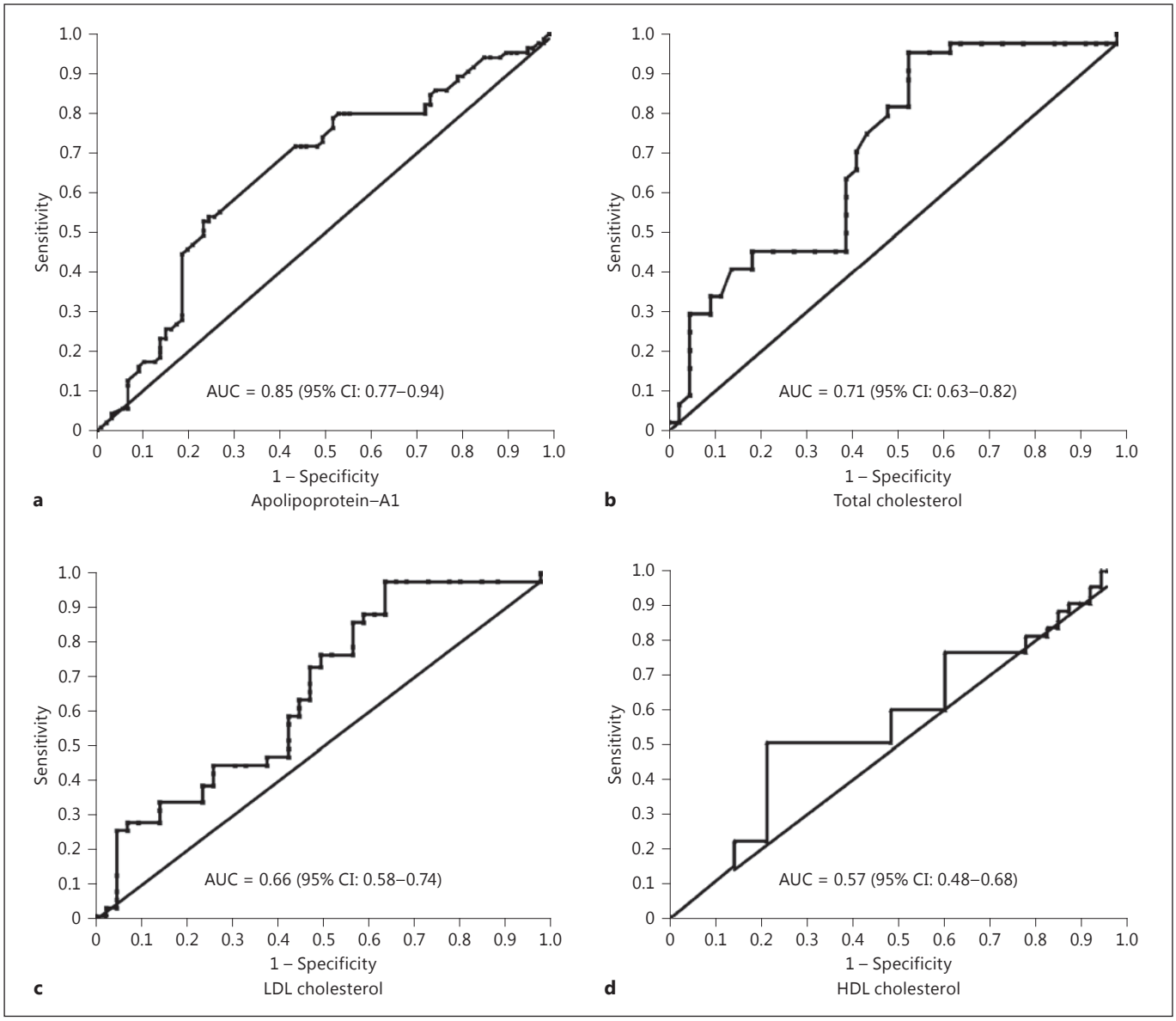

Fig. 1. Discrimination of CM from UM from analysis of the apolipoprotein-A1 and cholesterol levels. The AUC signifies the accuracy of the apolipoprotein-A1 and cholesterol levels for distinguishing CM from UM. An AUC value close to 1 indicates an excellent prediction of the disease. The reference (diagonal) line denotes an uninformative test, with an AUC of 0.50.

(table 3) revealed that in the CM group, total cholesterol was significantly lower by 33.9 mg/dl [95% confidence interval (CI) –57.1 to –10.6, p = 0.002], LDL by 38.5 mg/dl (95% CI –59.9 to –17.0, p < 0.001), HDL by 2.1 mg/dl and apolipoprotein-A1 by 38.8 mg/dl (95% CI –53.8 to –23.9, p < 0.001) compared with the control group. However, comparing the UM group with the controls, significantly lower values were recorded only for LDL (mean difference = 24.6 mg/dl, 95% CI –46.0 to –3.1, p = 0.019) and apolipoprotein-A1 (mean difference = 25.3 mg/dl, 95% CI –23.9 to –10.3, p < 0.001). Notably, the mean levels of plasma triglycerides were not significantly different among any of the pair-wise comparisons. The Spearman rho correlations of levels of malaria parasitaemia and plasma lipids are shown in table 4. Only apolipoprotein-A1 levels were low and significantly inversely correlated with the malaria parasite counts in both the UM and CM groups.

Accuracy of the Lipids and Apolipoprotein-A1 for Differentiating CM from UM

The area under the ROC curve (AUC) indicates the accuracy of different cholesterols and apolipoprotein-A1 to distinguish CM from UM. The ROC curves demonstrated apolipoprotein-A1 (AUC = 0.85; $p < 0.001$; fig. 1a), total cholesterol (AUC = 0.71; $p < 0.001$; fig. 1b) and LDL cholesterol (AUC = 0.66; $p < 0.001$; fig. 1c) to be good predictors of complicated *P. falciparum* malaria, while the predictive value of HDL cholesterol (AUC = 0.57; $p = 0.107$; fig. 1d) was not statistically significant. For apolipoprotein-A1, a cut-off value of 94.6 mg/dl had a specificity and sensitivity of 92.0 and 85.0%, respectively. Total cholesterol exhibited a moderate sensitivity (68.0%) and specificity (87.0%) for CM at a cut-off value of 87.5 mg/dl while LDL cholesterol, at a cut-off value of 5.3 mg/dl, provided 55.0% specificity and 52.0% sensitivity in predicting CM.

Discussion

The major finding of this study was that the level of apolipoprotein-A1 was remarkably lower in malaria patients than in healthy children and the serum level was inversely correlated with the degree of parasitaemia. This is consistent with the findings of previous studies [15–18]. The magnitude of the differences in the level apolipoprotein-A1 levels was also greater in the CM group than in the UM group. The effect of malaria on lipids and apolipoprotein-A1 is expected to become more pronounced as age increases [4], but this trend was not demonstrated by our data and the reason for this is unclear. However, our data suggest that the observed lower serum lipid profile in malaria patients (vs. controls) could be specific for *P. falciparum* malaria infection. Specifically, the findings of lower total cholesterol, HDL and LDL in the children with malaria compared with healthy controls corroborated earlier reports [15–18, 22, 23]. One important fact that lends credence to this characteristic feature is that the decline in lipid profile observed among children with malaria appears to be significantly more pronounced than previously observed in any infection [26].

One plausible explanation for malaria patients having lower lipid levels than healthy children is the impairment of lipid synthesis and the excessive consumption of lipids by the parasites [27]. Lipids are synthesized in the liver, through which infective malaria sporozoites pass in order to enter the bloodstream. The parasite invades and resides in the liver cells [28]. In this exoerythrocytic stage, the malaria parasites divide until many mature tissue schizonts are formed. Thereafter, the merozoites are released from the liver into the bloodstream, initiating the erythrocytic stage. Within the erythrocyte, a single merozoite divides into several merozoites [28]. All these developments and cell divisions demand substantial amounts of proteins and lipids, such as cholesterol and lipoproteins, for processes like membrane formation. However, it is not clear from the literature 'what relationships exist between malaria parasites and lipid synthesis in the liver?' and 'whether or not malaria parasites are capable of producing essential lipids themselves or do they utilise the host lipids?' Another important question that remains unanswered is 'whether or not malaria parasites benefit from low serum lipids in the host environment?'

The ROC analyses of the serum levels of cholesterol and apolipoprotein-A1 differentiated the predictions for CM from those for UM, indicating that these levels are indeed potential surrogate markers for distinguishing CM from UM. Though our data showed that reduced serum lipids and apolipoprotein-A1 were characteristic of acute falciparum malaria, other factors may also be responsible for lowering these levels. Further research into the biological mechanisms may explain these aberrations and provide new knowledge on the role of lipids in the pathogenesis of malaria. Research will also present opportunities to explore the utility of apolipoprotein-A1 in the search for interventions for malaria. Nonetheless, the already-documented low levels of apolipoprotein-A1 that accompany *P. falciparum* infection are of significant potential value in the clinical diagnosis of malaria and the monitoring of recovery from malaria illness.

Our study has some limitations. First, the time that the reduced serum lipid profile took to recover among the malaria patients was not investigated. In some previous studies [4], the reduced lipid level was reported to have returned to normal slowly; in only one study was the level of cholesterol significantly lower in the malaria patients than in the control group a month after treatment. Past studies did not report the time to recover from the reduced serum apolipoprotein-A1. Second, we did not determine the effect that drugs like anti-malarials and adjunct therapy possibly have on lipids. It is thus difficult to completely rule out lipid-lowering effects of such drugs as a reason for the lower levels observed in this study.

Conclusion

In this study, reduced levels of serum lipids and apolipoprotein-A1 were characteristic of UM and CM in children younger than 5 years old.

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Disclosure Statement

There are no disclosures.

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