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Lipids Levels in Patients with Uncomplicated Malaria Due to *Plasmodium falciparum*

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Authors' contributions

This work was carried out in collaboration between both authors. Author JLFV designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Author JGBR performed laboratory analysis and managed the literature searches. Both authors read and approved the final manuscript

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ABSTRACT

Changes in lipid profile are common in adult patients with malaria, but only a few studies have evaluated such lipid abnormalities in uncomplicated falciparum malaria cases from the South America. This is a prospective study designed to evaluate transient lipid abnormalities in adults with uncomplicated falciparum malaria as well as to assess if the parasite count correlates with the lipid levels at admission. A total of 60 adult males were included in the study, of which 30 had the slide-confirmed infection by *P. falciparum*. Serial blood samples were collected at admission and on days 3, 14 and 43. Triglycerides, total cholesterol, high-density lipoprotein (HDL-c), and low-density lipoprotein (LDL-c) were measured by colorimetric methods. At admission, the levels of total cholesterol, LDL and HDL were significantly lower in malaria cases compared to healthy controls, but the levels of triglycerides were significantly higher in these patients. There are significant changes in lipid levels in the follow up. The lipid levels were not associated with the parasite count. In conclusion, there are significant lipid abnormalities in the adults with low levels of *P. falciparum* infection and mild signs and symptoms of the disease, which are not associated with parasitemia at admission.

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1. INTRODUCTION

Malaria by *P. falciparum* is still a relevant public health issue worldwide. In the Brazilian Amazon basin, approximately 15,000 cases occurred in 2015 [1]. Repeated episodes of the disease are common in this area, which confers to the native population a partial immunity, and only a few cases progress to severe illness with cerebral or renal impairment. Overall, patients have low parasite density and mild signs and symptoms [2-4]; however, laboratory abnormalities are often reported in the acute phase of the disease, such as anaemia, thrombocytopenia, hypoglycaemia, and of the lipid profile [5-7].

The latter is common in the acute or chronic phases of infectious or inflammatory diseases [8,9]. Low levels of total cholesterol, high-density lipoproteins (HDL-c) and low-density lipoproteins (LDL-c) accompanied by high levels of triglycerides and very low-density lipoproteins (VLDL-c) characterize the lipid changes in malaria. Such abnormalities are transient; occur in the most prevalent species of Plasmodium as well as in complicated and non-complicated cases [10-15].

Despite the high occurrence of malaria in Amazon basin, only a few studies reported lipid changes in this endemic setting. Evaluation of the lipid abnormalities in the course of malaria in areas with high transmission rates is relevant since a long-term change in lipid profile can directly influence the risk of coronary disease and other related diseases [13-15]. Moreover, genetic ancestry influences the lipid profile of admixed population as that from South American that has different contributions of European, African and Amerindian ethnic ancestries [16-18]. Thus, the present study aims to evaluate the temporal changes in lipid profile of adults from Brazilian Amazon basin with uncomplicated malaria by *P. falciparum* and to assess if the parasite count correlates with the lipid levels at admission.

2. MATERIALS AND METHODS

2.1 Ethical Statement

The study was submitted to Plataforma Brasil under protocol CAAE 2 07199612.0.0000.0018, and approved under the number 261.593/2013. Informed written consent was obtained from all participants.

2.2 Study Site and Participants

This was a prospective study carried out in Anajas at the Marajo Island. The municipality has an area of 6,912 Km^2 and 27,540 inhabitants. The economy is based on agriculture practices, timber extraction, and fishing. The municipality accounts for 17.4%of malaria cases in the state of Para and has a constant annual incidence of cases above 50/1,000 inhabitants. The municipality have seven health public facilities, including an ambulatory for diagnosis and treatment of malaria.

Participants were randomly recruited among those who searched for attendance at Malaria Ambulatory of the municipality with signals and symptoms suggestive of malaria. Two groups of male adults were included in the study: (1) case: male adults with slide-confirmed infection by *P. falciparum* and (2) control: male adult with a negative diagnosis of malaria after microscopic examination of three blood smears. Exclusion criteria included patients with mixed malaria or signs and symptoms of severe malaria (jaundice, renal or pulmonary impairment, severe anaemia, altered levels of consciousness), parasitemia above 4%, chronic and other parasitic diseases, overweight and underweight individuals assessed by the body mass index. Individuals of the control group who referred history of malaria infection within the previous twelve months also were excluded from the study.

2.3 Treatment and Follow-up

Patients with malaria were treated with mefloquine and artesunate according to the recommendation of the World Health Organization [19]. The clinical staff of Malaria Ambulatory was responsible for prescribing and dispensing the anti-malarial drugs. The patients received specific instructions about the administration on each day and were strongly recommended to complete the course of treatment. Data regarding the clinical signals and symptoms and the history of malaria, including the last episode of the disease, were carefully recorded in an appropriate questionnaire during the enrolment of patients in the study. All patients were requested to return for follow-up on days 3, 14 and 43 or at any time that signs and symptoms suggestive of malaria occurred. A parasite count was performed at each visit.

2.4 Blood Sampling and Laboratory Analysis

Serial blood samples were collected in both groups recruited for the study on days 0, 3, 14 and 43. Samples were collected after a fasting of 12 h. Triglycerides, total cholesterol, HDL and LDL were measured by colorimetric methods using Roche-Diagnostic Kits in a Cobas c 111-Roche ™, following the good laboratory practices [20]. All blood samples were analysed in triplicate. The normal ranges of each lipid followed the recommendations of the Brazilian Cardiology Society [21].

2.5 Microscopic Examination

Parasite counts were done every 24 hours in Giemsa-stained thick films until clearance. Blood films were examined microscopically using 100X (oil immersion) objectives. Parasite density was expressed as the number of parasites per microliter of blood. This was derived from the number of parasites per 200 white blood cells in a thick film, considering a total white blood cell count of 8,000. The limit of detection of parasites was 40/µL [22].

2.6 Data Analysis

Data are presented as a mean, standard deviation and confidence interval. The Student t-test was used to compare lipid levels between cases and controls on D0. A univariate analysis was used to compare lipid levels amongst days of blood sampling in patients with malaria. The Pearson coefficient of correlation was used to estimate the correlations between parasitemia with triglycerides, total cholesterol, and fractions on D0. Data were analysed using SPSS software, Release21 (IBMinc, Chicago, IL, EUA). The accepted significance level was 5%.

3. RESULTS

A total of 60 male adults met the criteria for the inclusion in the study. The cases of malaria corresponded to 50% (n=30) of the participants. All cases reported previous episodes of the disease. Moreover, all cases showed low parasite count and mild signals and symptoms. The baseline characteristics of participants are in Table 1.

The mean total cholesterol level of the cases on D0 was 116 mg/dl (95% CI 103–129 mg/dl), on D3 was 118 mg/dl (95% CI 108–127 mg/dl), on D14 was 144 mg/dl (95% CI 135–152 mg/dl) and on D43 was 157 mg/dl (95% CI 147–168 mg/dl). The univariate analysis showed significant changes in cholesterol levels amongst days of the study, with the lowest values on days 0 and 3 ($F=14.95$, $p<0.001$). The healthy controls showed total cholesterol mean level of 174 mg/dl (95% CI 162–186 mg/dl), which was significantly higher than the cases on D0 ($t=6.652$, $p<0.0001$). Although the mean total cholesterol level increased in the follow-up of the cases, they were still below the controls on D43 ($t=2.181$, $p=0.033$). On D0, there was no significant correlation between the parasitemia and the total cholesterol ($r=0.2$, $p=0.209$).

The mean HDL-c level of the cases on D0 was 16.3 mg/dl (95% CI 11.9–20.6 mg/dl), on D3 was 17.4 mg/dl (95% CI 14–20.8 mg/dl), on D14 was 30 mg/dl (95% CI 27.3–32.4 mg/dl) and on D43 was 35 mg/dl (95% CI 31–37.2 mg/dl). The univariate analysis showed significant changes in HDL-c levels amongst days of the study with the lowest values on Days 0 and 3 ($F=28.69$, $p<0.001$). The healthy controls have an HDL-c mean level of 46.3 mg/dl (95% IC 41–51 mg/dl), which was significantly high than the cases on

Table 1. Baseline characteristics of participants

Characteristic	Cases (n=30)	Controls (n=30)	*p*-value
Age, years	33(11)	34(12)	0.521
Parasitemia at admission, geometrical mean	3178 (7.1)		
Previous episodes of disease, number of cases (%)	60	0	<0.0001
Parasite clearance, hours	48 (20)		
Fever clearance, hours	24(12)		
Erythrocytes at admission, $x10^6$/ µl	4.29(0.79)	4.7(0.82)	0.836
Hematocrit at admission, %	36.4(6)	39 (5)	0.331
Hemoglobin at admission, g/dl	11.9(2)	12(2)	0.9
Platelets at admission, $x10^3$/µl	136.9(61,1)	240.1(48.2)	<0.001

** results are expressed as mean and standard deviation*

D0 (t=8.99, p<0.0001). The values of HDL-c of the cases increased in the follow-up, but they were still below the controls on D43 (t=4.12, p=0.001). At admission, there was no significant correlation between parasitemia and HDL-c levels (r=0.0734, p=0.699).

The mean levels of LDL-c of cases on D0 was 64 mg/dl (95% CI48–80 mg/dl), on Day 3 was 69 mg/dl (95% CI 55–82 mg/dl), on D14 was 95 mg/dl (95% CI 86–105mg/dl) and on D43 was 114 mg/dl (95% CI 104–125 mg/dl).The univariate analysis showed a significant difference amongst days of the study, with the lowest values on days 0 and 3 (F=14.54, p<0.0001). The healthy controls have an LDL-c mean level of 112 mg/dl (95% CI 102–121 mg/dl), which was significantly higher than the cases on D0 (t=5.25, p<0.0001). However, the LDL-cmean levels were similar to the healthy control on D43 (t=0.2914, p=0.7718). On D0, there was no significant correlation between parasitemia and LDL-c levels (r=0.1804; p=0.3402).

The mean level of triglycerides of the cases on D0 was 158 mg/dl (95% CI 135–181 mg/dl), on D3 was 152 mg/dl (95% CI 131–173 mg/dl), on D14 was 132 mg/dl (95% CI= 112–153 mg/dl) and on D43 was 122 mg/dl (95% CI 102–140 mg/dl). The univariate analysis showed a significant difference in triglyceride levels amongst days of the study (F=2.741; p=0.0464), with the highest values on days 0 and 3. The healthy controls had a mean level of 122 mg/dl (95% IC= 98–146mg/dl), which was significantly lower than the cases on D0 (t= 1.908, p=0.0615). (Fig. 1 and Fig. 2) Finally, there was no significant correlation between the parasitemia and the triglycerides levels on D0 (r= -0.2619; p=0.1622).

4. DISCUSSION

The temporal variation of lipid levels was examined in patients with uncomplicated malaria by *P. falciparum* from the South America. At admission, the levels of total cholesterol, HDL-c, and LDL-c were lower in malaria cases than in healthy controls. On the other hand, the levels of triglycerides were high in malaria cases compared to healthy controls. These data confirm that patients with malaria from the South America have significant changes in lipid levels in the acute phase of the disease, as well as such abnormalities, are similar to uncomplicated falciparum malaria cases from the Africa and the Asia [10-15].

Changes in lipid and lipoprotein levels occur in most patients with active infections caused by parasites, but the exact mechanism is unclear [8,9]. In malaria, such alterations are due to the Plasmodium, to human-related factors, or both [10,13,14,23,24]. Plasmodium does not have any biological pathway for sterol synthesis for their metabolic requirements, such as membrane or hemozoin formation, and the cholesterol is obtained from the exogenous and endogenous pathways of the human host [25,26].

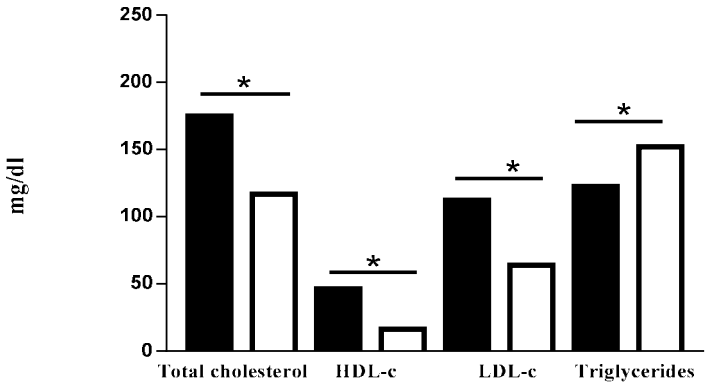

Fig. 1. Lipid levels in patients with uncomplicated falciparum (□) malaria at enrollment in the study (D0) and in the control group (■)

**p<0.05*

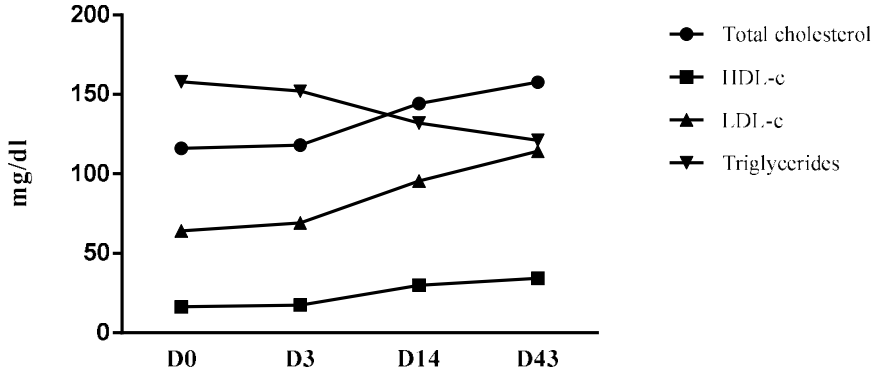

Fig. 2. Temporal variation of lipid profiles in patients with uncomplicated falciparum malaria

Abnormalities in triglycerides levels are probably due to the increase of VLDL production resulting from the excessive mobilization of free fatty acids from adipose tissue in response to stress due to the disease as well as to the impairment of the lipoprotein lipase system mediated through the levels of the tumor necrosis factor. After the clearance of parasites from blood, the triglycerides levels decreased to values similar to the controls. Regard to the total cholesterol and cholesterol-rich lipoproteins, the most significant impact of malaria was on HDL-c. The probable causes are the increased rate of HDL-C removal by Plasmodium, activation of the reticuloendothelial system leading to non-specific uptake of HLD-c in the phagocytic cell and oxidation of lipoproteins due to redox imbalance caused by the disease and by antimalarial drugs [27-33].

Studies evaluating transient changes in lipid profiles of malaria patients have shown inconclusive results, ranging from a few days to one year [10,12,15]. In the study, the levels of lipids changed differently after the clearance of parasites at 48 hours, as for instance, triglycerides levels decreased rapidly in malaria patients with values similar to healthy controls on Day 3, but LDL-c, HDL-c and the total cholesterol levels increased slowly during follow-up. In fact, the total cholesterol and HDL-c levels remained significantly lower than to the healthy controls on Day 43.

These changes in lipid profiles in the follow-up can be related to both the clearance of parasites and the improvement of the nutritional status of patients in the convalescence period [9,10,12,31]. Moreover, there were no significant correlations between the parasitemia at admission and the lipids levels. A plausible explanation is the low parasite density at admission in the study.

5. CONCLUSION

The data of the current study are relevant in the clinical spectrum of uncomplicated falciparum malaria cases, since they confirm the occurrence of transient changes in lipid levels, with highest abnormalities in the high-density lipoprotein levels. Finally, there are no significant correlations between parasitemia at admission and lipids levels.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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