

Full Length Research Paper

Serum lipid profile and hepatic dysfunction in moderate *Plasmodium falciparum* infection

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Plasmodium falciparum is one of four distinct species of the malaria parasite that afflict humans and pose a threat to public health. The present study seeks to ascertain the serum lipid profile and associated hepatic dysfunction of male subjects with moderate *P. falciparum* infection. The patients were adults ($n = 11$) of 21 to 31 years old and adolescent ($n = 10$) of 11 to 20 years old. Measurement of parasite density of peripheral blood smear was by Giemsa stained techniques. Serum lipid profile, bilirubin concentration, aspartate and alanine transferases activities were measured by spectrophotometric methods. Serum lipid profile of non-malarious and malarious subjects within the age brackets of 11 to 20 years showed no significant difference ($p > 0.05$); with exception of serum low density lipoprotein cholesterol (LDL-C) = 30.90 ± 7.10 mg/dl and high density lipoprotein cholesterol (HDL-C) = 31.10 ± 7.12 mg/dl ($p < 0.05$) of malarious subjects, which were below reference intervals. Specifically, for subjects within age brackets of 21 to 31 years, (aspartate aminotransferase, AST)_{non-malarious} = 15.32 ± 1.06 U/L, whereas, [AST]_{malarious} = 15.34 ± 0.95 U/L; $p > 0.05$. Also, (alanine transaminase, ALT)_{non-malarious} = 5.13 ± 1.88 U/L and [ALT]_{malarious} = 5.87 ± 3.00 U/L; $p > 0.05$, in subjects within age brackets of 11 to 20 years. Serum conjugated bilirubin (CB) concentrations of non-malarious and malarious subjects were within the range of 0.17 ± 0.06 to 0.41 ± 0.06 mg/dl; reference interval = 0.1 to 0.4 mg/dl; $p > 0.05$. Contrary, serum TB concentrations of corresponding malarious subjects gave values above the reference intervals ($p < 0.05$). The present study showed moderate *P. falciparum* infection caused profound changes in serum HDL-C and LDL-C levels that was not dependent on the age brackets of the individuals and did not cause profound hepatic dysfunction in the various subjects. Similarly, the two categories of malarious subjects did not present biliary obstruction but had jaundice by virtue of their raised serum levels of TB.

Key words: Serum, lipid profile, hepatic dysfunction, *Plasmodium falciparum*, malaria.

INTRODUCTION

Parasitic protozoa are responsible for some of the most devastating and prevalent diseases of humans since time immemorial. *Plasmodium falciparum* is one of four distinct species of the malaria parasite that afflict humans and pose a threat to public health. According to World

Health Organization (WHO) (2008), approximately 350 to 500 million cases of malaria infections occur in Sub-Saharan Africa, along with 110 million cases of illness and 2 million deaths of which 25% leads to childhood deaths (Adekunle et al., 2007; Onyesom et al., 2010).

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Malarial infection is associated with life threatening and debilitating conditions such as fever, chills, myalgia, headache, nausea, vomiting and diarrhea (WHO, 2008).

Lipoproteins such as chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL) and free fatty acids (FFA) are major lipid components in plasma. Most plasma apolipoproteins, endogenous lipids and lipoproteins have their origin from the liver (Tietge et al., 1998; Jiang et al., 2006; Mayes and Botham, 2003), which depends on cellular integrity and functionality of the hepatocytes. Under normal physiological conditions, liver ensures homeostasis of lipid and lipoprotein metabolism (Jiang et al., 2006). Hepatocellular damage often associated with severe and acute *P. falciparum* infections impairs these processes, leading to alterations in plasma lipid and lipoprotein patterns (Faucher et al., 2002; Sibmooh et al., 2004). Likewise, hyperbilirubinemia, increased plasma levels of aspartate transferase (AST) and alanine transferase (ALT) activities are strong evidence of gross hepatocytic dysfunction in patients with *P. falciparum* infection (Kochar et al., 2003; Uzuegbu and Emeka, 2011; Onyesom and Onyemakonor, 2011).

Relationships between serum lipid profile and severity of *P. falciparum* and other parasitic infections in human has drawn the attention of various research authors (Bansal et al., 2005; Siagris et al., 2006; Maekawa et al., 2011; Ramcharran et al., 2011) and has been proposed as a basis for diagnosis and severity of the disease (Baptista et al., 1996). However, most reports available in literatures are concerned with severe and acute malarial infection (Sibmooh et al., 2004; Akanbi et al., 2012; Akanbi, 2013). Therefore, the present study seeks to investigate the serum lipid profile and associated hepatic dysfunction of male subjects with moderate *P. falciparum* infection.

MATERIALS AND METHODS

Selection of subjects

Twenty-one (21) clinically confirmed malarious according to WHO (2008) and 12 h fasting male patients attending clinic at the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria and asymptomatic/non-malarious fasting male subjects {adolescent ($n = 15$); adult ($n = 15$)} enrolled for this study. The patients were in the following categories: adults ($n = 11$) of 21 to 31 years old and adolescent ($n = 10$) of 11 to 20 years old. The subjects were randomly selected between June and August, 2012. Exclusion criteria include; gastrointestinal tract infection, protein energy malnutrition, renal diseases, cirrhosis, hepatitis, obstructive jaundice, cancer, diabetes mellitus, hypertension, obesity, smoking, alcoholism, persons living with human immunodeficiency virus (HIV), patients taking anti-malaria drugs and vitamin supplements, patients who have treated malaria in the past 2 months (Onyesom and Onyemakonor, 2011; Idonije et al., 2011) and patients with low or high parasitemia.

Ethics

The Ethical Committee of University of Port Harcourt, Port Harcourt, Nigeria, approved the study in compliance with the Declaration on the Right of the Patient (WMA, 2000). Before enrolment for the study, the patients/subjects involved signed an informed consent form.

Collection and preparation of blood specimen

Blood specimen was collected by venipuncture at the end of the fasting period from subjects using 5.0 ml capacity disposable syringes. Four milliliter (4.0 ml) of the blood samples were transferred into plain bottles to allow for coagulation, whereas the remaining 1.0 ml was transferred into ethylenediaminetetraacetic acid (EDTA) bottles for malaria parasite tests. The coagulated blood samples were centrifuged at 3000 rpm for 10 min, the serum transferred into Bijou bottle and stored frozen until required for biochemical analyses (Onyesom et al., 2010).

Malaria parasite density test

Measurement of parasite density of peripheral blood smear was by Giemsa stained techniques. The films were examined microscopically using $\times 100$ objective under oil immersion (Cheesbrough, 1998). According to Idonije et al. (2011), level of parasitemia was graded as low+ (1 to 999/ μ l), moderate++ (1000 to 9999/ μ l) and severe+++ (> 10,000/ μ l).

Lipid profile assays

Total cholesterol (TC), triacylglycerol (TG) and high-density lipoprotein cholesterol (HDL-C) were determined using commercial kits (Randox Laboratory Ltd., UK). LDL-C concentration was determined by difference according to the formula described by Friedewald et al. (1972), as reported by Oluba et al. (2012). Very low-density lipoprotein cholesterol (VLDL-C) concentrations were estimated using the methods of Burnstein and Sammaile (1960) where the value in mg/dl is based on the assumption that in fasting subjects, the VLDL-C to total plasma TG ratio is relatively fixed at 1:5 (Ibegbulem and Chikezie, 2012).

Enzyme assay

Aspartate and alanine transaminases (AST and ALT) activities were measured by methods of Reitman and Frankel (1957) as reported by Onyesom (2012).

Bilirubin assay

Serum bilirubin was measured by the method as described by Enemor et al. (2005).

Statistical analyses

The experiments were designed in a completely randomized method and data collected were analyzed by the analysis of variance procedure while treatment means were separated by the least significance difference (LSD) incorporated in the statistical

Table 1. Serum lipid profile of non-malarious and malarious subjects.

Parameter (mg/dL)	NM		M		Reference Intervals*
	11-20 years	21-31 years	11-20 years	21-31 years	
TC	121.20±8.80 ^a	144.68±6.35 ^b	123.30±4.80 ^{a,c}	155.02±8.00 ^{b,d}	120-240
HDL-C	47.00±9.35 ^a	61.02±2.64 ^b	31.10±7.12 ^{a,c}	52.14±5.42 ^{b,d}	>40
LDL-C	67.80±6.80 ^a	117.14±5.69 ^b	30.90±7.10 ^c	96.60±8.35 ^{b,d}	60-160
VLDL-C	12.26±4.30 ^a	22.93±6.76 ^b	13.57±5.21 ^{a,c}	24.39±5.31 ^{b,d}	8-30
TG	61.30±5.40 ^a	114.65±6.96 ^b	67.89±7.20 ^{a,c}	121.95±5.63 ^{b,d}	40-150

*Liberopoulos et al. (2002). Means in the row with the same letter are not significantly different at $p > 0.05$ according to LSD. NM: Non-malarious; M: Malarious.

Table 2. Serum AST and ALT activities of non-malarious and malarious subjects.

Parameter (U/L)	NM		M		Reference interval*
	11-20 years	21-31 years	11-20 years	21-31 years	
AST	9.13±2.00 ^a	15.32±1.06 ^{a,b}	11.20±2.54 ^{a,b,c}	15.34±0.95 ^{a,b,c,d}	6-25
ALT	5.13±1.88 ^a	7.67±0.63 ^{a,b}	5.87±3.00 ^{a,b,c}	9.40±0.80 ^{a,b,c,d}	3-26

*Martin, (1983). Means in the row with the same letter are not significantly different at $p > 0.05$ according to LSD. NM: Non-malarious; M: Malarious.

analysis system (SAS) package of 9.1 version (2006). The correlation coefficients between the results were determined with Microsoft Office Excel, 2010 version.

RESULTS

An overview of Table 1 showed that serum lipid profile of non-malarious subjects (control) between the age brackets of 11 to 20 and 21 to 31 years were generally within reference intervals. The lipid parameters were relatively higher in individuals within age brackets of 21 to 31 years ($p < 0.05$). Similarly, serum TC of malarious subjects (11 to 20 years) was within reference intervals and was not significantly different ($p > 0.05$) from non-malarious counterparts. Lipid parameters of non-malarious and *P. falciparum* infected individuals within the age brackets of 11 to 20 years showed no significant difference ($p > 0.05$); with exception of serum [LDL-C] = 30.90 ± 7.10 mg/dl and [HDL-C] = 31.10 ± 7.12 mg/dl ($p < 0.05$) of malarious subjects, which was below reference intervals. Likewise, serum lipid profile of malarious and non-malarious subjects within the age brackets of 21 to 31 years exhibited no significant difference ($p > 0.05$). Serum concentrations of HDL-C ($p > 0.05$) and LDL-C ($p < 0.05$) of the two age brackets of malarious subjects were lower than corresponding non-malarious individuals.

Table 2 showed that serum levels of AST and ALT of non-malarious and malarious subjects, irrespective of age categories, were not significantly different ($p > 0.05$). Although serum levels of the two enzymes were within

reference intervals, AST and ALT activities of non-malarious and malarious subjects (21 to 31 years) were higher ($p > 0.05$) than those of age brackets of 11 to 20 years. Specifically, for subjects within age brackets of 21 to 31 years, $[AST]_{\text{non-malarious}} = 15.32 \pm 1.06$ U/L, whereas, $[AST]_{\text{malarious}} = 15.34 \pm 0.95$ U/L; $p > 0.05$. Also, $[ALT]_{\text{non-malarious}} = 5.13 \pm 1.88$ U/L and $[ALT]_{\text{malarious}} = 5.87 \pm 3.00$ U/L; $p > 0.05$, in subjects within age brackets of 11 to 20 years.

Serum CB concentrations of non-malarious and malarious was within the range of 0.17 ± 0.06 to 0.41 ± 0.06 mg/dl; reference interval = 0.1 to 0.4 mg/dl, $p > 0.05$ (Table 3). However, the range of serum TB concentrations of non-malarious subjects of the two age categories was within normal physiologic concentration. Contrary, serum TB concentrations of corresponding malarious subjects gave values above reference intervals ($p < 0.05$) (Table 3). Serum lipid profile of the various experimental groups showed strong positive correlations. The lowest correlation ($r = 0.799637$) was exhibited between age brackets of (21 to 31 years) non-malarious and (11 to 20 years) malarious subjects (Table 4). Alterations in serum lipid profile were irrespective of the age brackets of the patients.

DISCUSSION

Serum lipid profile of asymptomatic/non-malarious fasting male subjects corresponded with the reference intervals as reported by Liberopoulos et al. (2002) (Table 1). The

Table 3. Serum bilirubin concentrations of non-malarious and malarious subjects.

Parameter (mg/dl)	NM		M		Reference Interval*
	11-20 years	21-31 years	11-20 years	21-31 years	
CB	0.17±0.06 ^a	0.36±0.89 ^{a,b}	0.24±0.07 ^{a,b,c}	0.41±0.06 ^{a,b,c,d}	0.1-0.4
TB	0.23±0.03 ^a	0.62±0.06 ^{a,b}	2.17±0.17 ^c	3.12±0.11 ^{c,d}	< 1.0

*Martin, (1983). CB = conjugated bilirubin, TB = total bilirubin, Means in the row with the same letter are not significantly different at $p > 0.05$ according to LSD. NM: Non-malarious; M: Malarious.

Table 4. Correlations (r) of serum lipid profile of non-malarious and malarious subjects.

Age brackets of Subjects (years)	(11-20 years) NM	(21-31 years) NM	(11-20 years) M	(21-31 years) M
(11-20) NM	1.000000	-	-	-
(21-31) NM	0.921394	1.000000	-	-
(11-20) M	0.911751	0.799637	1.000000	-
(21-31) M	0.927869	0.97113	0.903284	1.000000

NM: Non-malarious; M: Malarious.

relatively higher serum lipid concentration in individuals within age brackets of 21 to 31 years ($p < 0.05$) was a reflection of age dependent adjustments in the pattern of lipid metabolism (Yoshida et al., 2007; Parini et al., 1999). According to Parini et al. (1999), elevated levels of plasma TC, particularly LDL-C, are associated with enhanced risk for atherosclerosis and coronary heart disease. However, the present study showed that the two categories of asymptomatic/non-malarious male subjects did not present hyperlipidemia.

Relationship between serum cholesterol levels in man/animals and parasitic infections has drawn the attention of several authors (Mohanty et al., 1992; Bansal et al., 2005; Adekunle et al., 2007; Liberopoulos et al., 2002; Durgut et al., 2012). Marginal increase in serum levels of TC in malarious subjects ($p > 0.05$) (Table 1), showed a departure from those previously reported in human with severe and acute malarial infection (Griffiths et al., 2001; Ogbodo et al., 2008), mice inoculated with *Plasmodium yoelli* (Adekunle et al., 2007), patient with *Visceral leishmaniasis* (Liberopoulos et al., 2002) and dogs with symptomatic *V. leishmaniasis* (Durgut et al., 2012) infections. Mohanty et al. (1992) had earlier posited that serum level of TC is reduced in low-level malarial infection, which is in concord with the present report.

In another report, Sibmooh et al. (2004) noted that serum levels of VLDL-C and HDL-C were significantly higher in malaria than in control subjects. They further noted that oxidized LDL-C from malarial patients increased the endothelial expression of adhesion molecules. In contrast to the present findings, in moderate malaria

infection, serum levels of LDL-C and HDL-C were lower than in control subjects (Table 1). These observations suggest the critical role of oxidized lipoproteins, especially LDL-C on the pathogenesis of malaria. In addition, moderate malaria infection was associated with reduced serum levels of VLDL-C and HDL-C (Table 1) that was in conformity with previous report of Mohanty et al. (1992). From another report, the findings of the present study (Table 1) coincided with that of Faucher et al. (2002). They reported that malaria infection produces moderate changes in plasma lipid profile in man, with typical decline in HDL-C concentration. It is worthwhile to note that Ogbodo et al. (2008) posited that oxidative modification of HDL-C and reduced serum levels of this class of lipoprotein was associated with the pathophysiology of malaria.

According to Leonarduzzi et al. (2000), levels of oxidative modifications of the various lipoproteins showed a relationship with severity of malaria infection. Thus, fluxes in serum lipoprotein concentrations are pointer to the fact that severity of malarial infection dictated the pattern of serum lipoproteins (Baptista et al., 1996). These changes in lipid parameters are more pronounced in *P. falciparum* infection (Sibmooh et al., 2004). The marginal increases in serum TG concentrations in the various experimental subjects ($p > 0.05$) (Table 1) was consistent with the reports of individuals with low-level malarial infection (Mohanty et al., 1992), malarial infection in children (Ogbodo et al., 2008), parasitic protozoa infection (Vial et al., 2003) and in animal model infected with *P. Yoelli* (Adekunle et al., 2007).

Likewise, in agreement with the present findings, there

are reports on raised serum levels of TG in animals with *V. leishmaniasis* infection (Liberopoulos et al., 2002; Durgut et al., 2012) and Monkeys infected with *Diplococcus pneumoniae* and *Salmonella typhimurium* (Fiser et al., 1972). In contrast, Mohanty et al. (1992) noted that serum levels of TG were lower in patients than in the control group. However, the difference was significant only for those with severe malaria ($p < 0.001$). They further reported that the levels of all the other plasma lipids were significantly higher ($p < 0.001$) in those with severe malaria than in those with moderate malaria compared with the control group.

Over three decades ago, Beach et al. (1977) had previously proposed that there was no indication from their studies that increase in serum lipid was due to the lipid content of the parasite. The alterations in serum lipid profile of malarious subjects could be attributable to the level of haemolysis in malaria, which is proportional to severity of infection (Baptista et al., 1996). Since the erythrocyte membranes are predominantly lipid in composition, the liberation of membrane lipids following sustained haemolysis accounted for the observed alterations in the serum lipid profile of patients presenting this disease (Garba et al., 2004). Furthermore, parasitized parenchymal and Kupffer cells compromise lipid metabolism engendering distortions in lipoprotein particles synthesized by the liver with associated alterations in plasma lipid profile (Oluba et al., 2012).

Serum levels of AST and ALT as well as TB and CB gave insights into the integrity and functional status of hepatocytes. Serum levels of the two enzymes (AST and ALT) are non-specific test to ascertaining hepatic dysfunction because they have their origins from other extra-hepatic tissues. However, elevated serum level of ALT is more specific for hepatic dysfunction. Accordingly, serum levels of conjugated bilirubin (TB) and conjugated bilirubin (CB) was measured for confirmatory diagnosis. Serum levels of AST and ALT of the experimental subjects (Table 2) were within corresponding reference intervals according to Martin (1983). This was an indication that moderate malarial infection did not cause profound hepatic dysfunction. Similarly, the serum level of CB was not significantly ($p > 0.05$) raised in the two categories of malarious subjects (Table 3). Therefore, patients with moderate malarial infection did not present biliary obstruction (Murray, 2003). However, the patients had jaundice by virtue of their raised serum levels of TB (Kochar et al., 2003).

Hepatic dysfunction in *P. falciparum* malaria manifested in form of jaundice is one of the important features of malaria. The etiology of hepatic dysfunction in patients with *P. falciparum* malaria is multifarious and has been described elsewhere (Maegraith, 1981; Cassidy and Reynolds, 1994; Kochar et al., 2003; Garba and Ubom, 2005). The present study showed that moderate *P.*

falciparum infection caused profound changes in serum HDL-C and LDL-C levels that was not dependent on the age brackets of the individuals and did not cause profound hepatic dysfunction in the various subjects. Similarly, the two categories of malarious subjects did not present biliary obstruction but had jaundice by virtue of their raised serum levels of TB.

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