Journal of Medical and Biological Science Research
Vol. 2 (10), pp. 158-162, December, 2016
ISSN: 2449-1810
Full Length Research Paper
http://pearlresearchjournals.org/journals/jmbsr/index.html

Incidence and Evaluation of Stress Induced In *Plasmodium Falciparum* Malaria Infected Individuals Using Cortisol, Malondialdehyde, Blood Glucose and Lipid Profile Level

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Accepted 12 August, 2016

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ABSTRACT

The aim of this study was to evaluate stress induced in *Plasmodium falciparum* malaria parasite infected individuals using cortisol, malondialdehyde, blood glucose and lipid profile level. The study was conducted at Federal Teaching Hospital, Ido-Ekiti, Nigeria. Two hundred and two blood samples were collected twice from the same malaria infected individuals; the patients were placed on artemether and lumefantrine combine therapy. Thick blood film was made from EDTA blood sample and stained with Giemsa staining technique for malaria parasite detection, the procedure was described by routine manual method. Cortisol was estimated using Enzyme Linked Immunosorbent Assay method by Monobind Inc. Malondialdehyde (MDA) was estimated using thiobarbituric acid method by Tomotsu; blood glucose level was estimated using glucose oxidase method and blood lipid profile was also estimated using randox kit. Data obtained was analyzed using SPSS version 16. The mean ± SE of cortisol, MDA, blood glucose, low density lipoproteins (LDL) and triglyceride in pre treatment were significantly ($p<0.05$) higher compared to post treatment and control (in each case). This study shows that *Plasmodium falciparum* malaria induces stress especially in acute malaria infected individuals. However, during malaria treatment, the level of stress induced by malaria parasite was decline as the clinical condition improves due to the effect of anti-malaria drug used as observed in the study.

Key Words: Malaria parasite, Stress induced and Anti-malaria therapy.

INTRODUCTION

Stress contributes to the development of disease processes through prolonged elevation of a number of hormones. Stress induction rise in corticotropin releasing hormone (CRH) which directs the pituitary gland to produce adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal glands to produce and release cortisol (Pagana et al., 1998). Cortisol is a hormone that plays a role in the metabolism of proteins, lipids and carbohydrates. It affects blood glucose levels, helps maintain blood pressure and helps regulate the immune system. Severe *Plasmodium falciparum* malaria has been associated with an increase in oxidative stress, in relation with disease severity (Parker et al., 1985; Chrousos, 1995). Malaria infection especially *P. falciparum* is associated with malondialdehyde causing reduction in antioxidant capacity in infected patients. *Plasmodium* infected human erythrocytes are under increased oxidative stress exerted by the malaria parasite which generate reactive oxygen species within the erythrocytes, resulted to immune activation in the host and damage some uninfected erythrocytes (Rath et al., 1991; Golenser et al., 1991a,b). Glucose metabolism during malaria infection is affected by several factors which include anti-malaria drug, fever, parasite metabolism, hormonal changes, cytokines, fasting and gastrointestinal disturbances (Davis et al., 1993; Davis et al., 2002). During malaria parasite infection, glucose is rapidly taken up across the parasite plasma membrane through a

facilitated hexose transporter and is in turn metabolized through the process of glycolysis (Woodrow et al., 1999). Liver ensures homeostasis of lipid and lipoprotein metabolism, 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). Cholesterol is synthesized in the liver which happens to be the major site of *plasmodium* infection and this raises some questions whether there is any relationship between the cholesterol synthesis by the liver and the *plasmodium* infection of the liver (Esan, 2014).

The alterations in serum lipid profile of malaria individuals could be attributable to the level of haemolysis in malaria, which is proportional to severity of infection (Baptisa 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; Esan, 2014). Artemisinins, especially artesunate and artemether have been shown to be a good source of antioxidants with very high oxygen radical absorbance capacity levels result in more rapid malaria parasite clearance by the release of high dose of free radicals that attack the cell membrane of the parasite in the presence of high iron concentration. It is safer and simpler to administer, it reduces parasite numbers by a factor of approximately 10,000 in each asexual cycle, which is more than other current anti-malarias and resulted in fewer episodes of hypoglycaemia than quinine (Dondorp et al., 2005). Malaria parasites accumulate iron by infecting iron rich red blood cells. Excess iron that spill onto the surrounding tissue will activate the drug to generate a burst of free radicals that attack the iron rich cells, killing the parasite in the process. The aim of this study was to evaluate serum cortisol, oxidative stress (malondialdehyde) exerted by the malaria parasite and determine its effect on blood glucose and lipid in malaria infected individuals before and after anti malaria drug treatment.

MATERIALS AND METHODS

Study Design

This was a cross sectional study conducted at Federal Teaching Hospital, Ido-Ekiti, Nigeria. After the patient has been clinically diagnosed for malaria infection and confirmed using malaria rapid kit, eight millimeters (8 mL) of blood samples were collected twice from two hundred and two (202) *P. falciparum* malaria infected adult individuals grouped as pre anti-malaria drug treatment (on the first day of visiting hospital). Another 8 ml of blood sample was collected on the second or third day from the same patient after taking anti-malaria drugs grouped as post anti-malaria drug treatment sample. Patients were placed on artemether and lumefantrine combination therapy (80/480 mg) taken one tablet two times daily for three days. Blood sample from one hundred and two (102) apparently healthy non-malaria infected individuals were collected as controls. Out of 8 ml of blood sample collected, 3 mL of blood sample was dispensed into plain bottles; serum was extracted to assay cortisol using enzyme linked immunosorbent assay (ELISA) method by MDA was estimated using thiobarbituric acid method by Tomotsu (Esan, 2015). 1ml of blood sample was dispensed into fluoride oxalate bottles to assay blood glucose level using glucose oxidase test method; 3 ml of blood sample was dispensed into lithum heparin bottle to assay blood lipid profile (high density lipoproteins (HDL), triglyceride, total cholesterol were estimated using randox kit while Low density lipoprotein was determined by Freidewald's formula). 1ml of blood sample was dispensed into di-potassium ethylenediaminetetracetic acid (K2EDTA) vacuum tubes for malaria parasite screening using commercially prepared malaria rapid test kit. Malaria parasite detection using thick blood film was stained with Giemsa's staining technique and thin blood films was also made with Leishman's staining technique for malaria parasite count and malaria parasite species identification were observed under x40 and x100 objectives lenses as microscopic gold standard diagnosis of malaria parasite infection (Esan and Titilayo, 2014; Esan, 2015). Questionnaire was used to obtain the demographic characteristics and other relevant information for the study.

Statistical Analysis

Data obtained were analyzed and presented as mean ± standard error (SE); significant test was done by ANOVA and t test. Level of significance was considered as <0.05.

RESULTS

The mean ± SE of cortisol 22.02 ± 5.09 in pre treatment was significantly ($p<0.05$) higher compared to 16.74 ± 6.51 and 6.60 ± 1.62 in post treatment and control respectively ($F = 289.54$ $p=0.00$). The mean ± SE of MDA 19.19 ± 4.28 in pre treatment was significantly ($p<0.05$) higher compared to 15.31 ± 5.62 and 8.32 ± 0.88 in post treatment and control respectively ($F = 199.54$; $p=0.00$). The mean ± SE of glucose 4.99 ± 1.11 in pre treatment was significantly ($p<0.05$) higher compared to 4.37 ± 0.87 and 3.60 ± 0.32 in post treatment and control, respectively ($F = 82.32$; $p= 0.00$). The mean ± SE of HDL 27.47 ± 3.44 in post treatment was significantly lower compared to 28.75 ± 6.51 and 42.08 ± 3.66 in pretreatment and control, respectively ($F = 329.36$; $p=0.00$). The mean ± SE of LDL 17.72 ± 1.25 in pre treatment was significantly ($p<0.05$) higher compared to

12.21 ± 0.86 and 6.89 ± 0.68 in post treatment and control, respectively (F = 21.40 p=0.00). The mean ± SD of triglyceride 22.02 ± 1.55 in pre treatment was significantly (p<0.05) higher compared to mean ± SE of triglycerides 17.61 ±1.24 and 11.63 ± 1.15 in post treatment and control, respectively (F = 41.42; p=0.00).
The mean ± SE of total cholesterol 96.88 ± 19.81 in pre treatment was significantly (p<0.05) lower compared to mean ± SE of total cholesterol 103.37 ±12.31 and 124.03 ±10.29 in post treatment and control, respectively (F = 106.41; p=0.00). Multiple comparison between pre treatment and post treatment show that mean ± SE of cortisol MDA, glucose, HDL, LDL, triglycerides were significantly (p<0.05) higher in pre treatment compared to mean ± SE values in post treatment while mean ± SE of total cholesterol in pre treatment was lower compared to mean ± SE in post treatment. Multiple comparison between pre treatment and control show that mean ± SE of cortisol, MDA, glucose, LDL and triglyceride were significantly (p<0.05) higher compared to mean ± SE in control while mean ± SE of HDL and total cholesterol were significantly (p<0.05) lower in pre treatment compared to mean ± SE in control. Multiple comparison between post and control show that mean ± SE of cortisol, MDA, glucose, LDL and triglyceride were significantly (p<0.05) higher compared to mean ± SE in control while mean ± SE of HDL and total cholesterol in post treatment were significantly (p<0.05) lower compared to mean ± SE in control. Table 1 show comparison of mean ± SE in cortisol (µg/dL), MDA (nmol/L), glucose (mmol/L), HDL (mg/dL), LDL (mg/dL), triglycerides (mg/dL) and total cholesterol (mg/dL) in pre, post anti-malaria drug treatment and control subjects.

DISCUSSION

Cortisol plays an important role in the immune response, by repressing and stimulating the immune system. It was reported that cortisol level is expected to be high in malaria infection before treatment due to the maintained stress and decline as the clinical condition is improved; according to previous study by Esan (2015) Ringwald et al. (1991) they reported that cortisol, MDA and blood glucose were higher in pre-treatment compared with post and control subjects in different haemoglobin variants among *P. falciparum* malaria parasite infected subjects, cortisol level will probably return to normal after treatment (Esan, 2015; Ringwald et al., 1991), similar to what observed in this present study, the level of cortisol in patients with high parasitemia was higher than that of patients with low parasitemia. Findings in this study support the facts that fever reflects a time of blood cell lysis, releasing parasite antigens into the circulation which in turn, induce the release of cytokines. These cytokines stimulate the thermo-regulatory centre in the hypothalamus as well as the HPA axis, this explained the high cortisol levels during pretreatment of malaria infection with schizogony therefore representing an acute stimulus of the HPA axis. Similarly, serum cortisol levels was reported on Days 0, 1 and 7, in patients infected with *P. falciparum*; higher mean concentration level of cortisol was observed on Day 0 followed by a significant reduction on Day 1 and a highly significant decline on Day 7 after treatment, they reported that there was significant rise in serum cortisol level of malaria patients compared to control and there was no significant difference between uncomplicated malaria infected patients and those with cerebral malaria, also there was no a single patient with cortisol level less than the mean level of controls during the seven days period of treatment (Tim et al., 1998; Rosana et al., 2006). Several studies have shown the relation between malaria-induced stress and the level of cortisol. Resumo (1998) reported that when persons experience stress, bodies release cortisol. He also reported that levels of cortisol in serum sample collected from malaria patients were significantly higher than those of normal subjects as also reported in this present study. He concluded that corticosteroid may interfere with initial response of *P. falciparum*-infected patients to treatment (Resumo, 1998).
The report of Muawia et al. (2009) is similar to result of cortisol in this present study, he reported that cortisol showed higher levels in the whole infected patients as one group and the two groups of patients compared to the control group (Muawia et al., 2009). Increase in cortisol level in malaria infection was explained and supported by Hilary (2002), he reported that infection with *P. falciparum* malaria increases the secretion of pro-inflammatory hormones and mediators which induce resistance to cortisol, such as tumor necrosis factors (TNFs) and antimicrobial agents, also the infection reduce the synthesis of cortisol receptors that increase plasma cortisol level (Hilary, 2002). It is also well known that the degree of parasitemia has effects on the immune system (Deans et al., 1983). In malaria infection, oxidative stress increases as more reactive oxygen species (ROS) are generated. *Plasmodium* infected human erythrocytes are under increased oxidative stress exerted by the malaria parasite. In this present study, the level of malondialdehyde in *P. falciparum* malaria infection was higher in pre-treatment and decreased during post treatment. Malondialdehyde level in control subjects were observed to be lower compared to values obtained in pre-treatment and post-treatment. However, the level of malondialdehyde in patients with high parasitemia was higher compared to patients with low parasitemia.
This study showed increased in malondialdehyde levels in patients with *P. falciparum* malaria infection which reflect the severity of malaria infection (Das et al., 1993; Hunt and Stocker, 1990). High MDA in malaria patients indicates that there is increased production of reactive

Table 1. Mean±SE of cortisol, MDA, glucose and lipid parameters in pre, post anti-malaria drug treatment in malaria infected subjects.

Groups	Cortisol µg/dL	MDA nmol/L	Glucose mmol/L	HDL mg/dL	LDL mg/dL	TRIG mg/dL	TOTAL CHO mg/dL
Pre-Treatment (N = 202)	22.02±5.09	19.19 ±4.28	4.99 ±1.11	28.75 ±6.51	17.72 ±1.25	22.02 ±1.55	96.88 ±19.81
Post-Treatment (N = 202)	16.74 ±6.51	15.31 ±5.62	4.37 ±0.87	27.47 ±3.44	12.21 ±0.86	17.61 ±1.24	103.37 ±12.31
Control (N=102)	6.60 ±1.62	8.32 ±0.88	3.60 ±0.32	42.08 ±3.66	6.89 ±0.68	11.63 ±1.15	124.03 ±10.29
F (P-value)	289.54 (0.00*)	199.54(0.00*)	82.32(0.00*)	329.36(0.00*)	21.40(0.00*)	41.42(0.00*)	106.41(0.00*)
(Pre-Treatment) VS (Post Treatment) p-value	0.00*	0.00*	0.00*	0.04*	0.00*	0.00*	0.00*
(Pretreatment) VS (Control) p-value	0.00*	0.00*	0.00*	0.00*	0.00*	0.00*	0.00*
(Post Treatment) Vs (Control) p-value	0.00*	0.00*	0.00*	0.00*	0.00*	0.00*	0.00*

P<0.05 significance, P>0.05 no significant, F (P-value) = mean ± SE of parameters compared using ANOVA.

oxygen species in these patients as indicated in this present study. Oxidative stress in malaria infection caused by *P. falciparum* is due to excess production of reactive oxygen species which create an increase in oxygen free radicals, causing failure in normal immune defense mechanism which increases the antioxidant blood serum levels (Hunt and Stocker, 1990; Egwunyenga et al., 2004). Malaria parasite stimulates certain cells to produce reactive oxygen species thereby resulting in hemoglobin degradation which is the major reasons for development of malaria anemia seems to be oxidative stress while changes in micronutrient metabolism alter disease progression and severity (Loria et al., 1999; Pradines et al., 2005; Das and Nanda, 1999; Kremsner et al., 2000; Singotamu et al., 2006). Highly increased MDA activity found in malaria positive patients is an indication of increased production of reactive oxygen species, On the degree of parasitaemia in relation to malondialdehyde level, it was observed that malondialdehyde level increases as the degree of parasitaemia increases from mild (+) to moderate (++) and to severe (+++) parasitaemia (Hunt and Stocker, 1990; Egwunyenga et al., 2004; Akanbi et al., 2009). Interestingly, report shows malaria parasite itself generates large quantities of ROS and also through its interaction with phagocytic cell system (Kremsner et al., 2000).

The oxidant stress originates due to destruction of red cells which cause imbalance between the generation of reactive oxygen species and the antioxidant defense system (Bonnefont-Rousselot et al., 2000; Mendis et al., 2001). Pathogenesis of an infecting agent cause an over production of free radical species and failure of normal defense mechanism that decreases antioxidant level which leads to decreases elimination of reactive substances. Malaria parasite is capable of generating reactive oxygen species within the erythrocytes and the ROS resulting from immune activation can further damage the uninfected erythrocytes (Rath et al., 1991) which cause an increase in oxidative stress as observed in this present study. In this present study, the result of blood glucose level in malaria infection was higher in pre-treatment and decreased during post treatment. Glucose level in control subjects were observed lower compared to value obtained in pre-treatment and post-treatment. During malaria parasite infection, glucose is rapidly taken up across the parasite plasma membrane through a facilitated hexose transporter and is in turn metabolized through the process of glycolysis (Woodrow et al., 1999). Earlier researcher reported that high plasma cortisol may stimulate gluconeogenesis in humans; increase in plasma glucose concentration supports the idea of a major role for cortisol in the stimulation of gluconeogenesis in patients with malaria (Dekker et al., 1997; Tayek and Katz, 1997). These facts supported the results of cortisol and glucose obtained in this present study. Decrease in blood glucose level during malaria treatments as observed in post-treatment can be due to several factors such as; drug treatment, fever, parasite metabolism, hormonal changes, cytokines, fasting and gastrointestinal disturbances. It was reported that *P. falciparum* parasites fully depend on glucose as an energy source, hence hypoglycemia occurs during the management of patients with malaria (Goodyer and Taraschi, 1997; Davis et al., 2002), it is well known that some anti-malaria drug stimulates diabetes relevant parameters, such as increased plasma insulin concentrations and hypoglycemia. However, contrary to this present study, studies by Goodyer and Taraschi (1997) Kayode et al. (2011) Onyesom and Agho (2011) Mizushima et al. (1994) Binh et al. (1997) reported hypoglycemia in malaria infected patients, stated host glucose production becomes insufficient for both host and parasite demand as infection progressed. Result of blood lipid profile in this study is a follow up and further studies of previous study by Esan (2014).

It was earlier reported that Lipoproteins are major lipid component in plasma and certainly targets for oxidative stress, it appears that the parasites take advantage of the oxidative stress to increase

its pathogenicity.

The rapidly growing malaria parasite requires large amounts of lipids for increase in surface area and volume of its internal membranes, certain serum lipid fractions may favour the onset and/or severity of malaria infection (Esan, 2014; Davis et al., 1993; Das et al., 1996; Mohanty et al., 1992). The increased oxidative stress in malaria, which accounts for the degradation of the lipoproteins, may originate from several sources including intracellular of parasitized erythrocytes and extracellular of haemolysed erythrocytes or host immune responses. During malaria infection, the levels of LDL and HDL are decreased while triglycerides are moderately increased. These events may be related to the oxidation, and they are in consistent with the fact that host response to acute infection increases lipoprotein oxidation *in vivo* (Esan, 2014; Memon et al., 2000).

CONCLUSION

This study showed that *P. falciparum* malaria induces stress especially in acute malaria infected individuals. However, during malaria treatment the level of stress induced by malaria parasite declined as the clinical condition improves due to the effect of anti-malaria drug used as observed in the study

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