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Effects of Antimalaria Drugs on Antioxidant Status of Malaria Patients

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Abstract: Malaria infection has been found to be associated with lipid peroxidation accompanying reduction in antioxidant capacity of the infected patients especially *Plasmodium falciparum* infection. Antimalarial drugs also affects the oxidative stress pattern of malaria patients. The effects of malaria infection and the antimalaria drugs, chloroquine, sulfadoxine-pyremethamine and artemisinin combination therapy of the oxidant (malondialdehyde, MDA) and antioxidant status (enzyme and non-enzyme) of malaria patients were investigated. The result showed that the level of MDA was significantly elevated ($p<0.05$) in malaria patients compared to the control subjects. The MDA levels of patients on drugs were also raised compared to the control subjects; chloroquine and fansidar had the highest level of MDA. The antioxidant status (enzyme and non enzyme) was significantly reduced ($p<0.05$) in malaria patients compared to the control subjects. These effects were dependent on the degree of parasitaemia, duration of illness and age of the malaria patients. An insignificant increase was however observed in patients on antimalaria drugs compared to patients who did not take any of the antimalarials. ACT was found to be a better antimalarial amongst the drugs tested, considering its antioxidant potency. Thus it can be inferred that indeed most antimalaria drugs act by increasing the oxidant stress level, hence they should be supplemented by antioxidants as part of treatment regime.

Key words: Malaria · Chloroquine · Sulfadoxine-pyremethamine · Artemisinin-Combination Therapy · Oxidative status

INTRODUCTION

Malaria is one of the most important public health issues affecting humanity today. Globally, millions of deaths attributable to malaria are still being recorded [1, 2]. The World Health Organization (WHO) estimates that 500 million new malaria infections occur worldwide with 110 million cases of illness and almost 2 million deaths with 25% of childhood deaths in Africa associated with malaria [3]. Malaria is a disease caused by protozoan parasite *plasmodium*. Human malaria is caused by four different species of *plasmodium*: *Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax and Plasmodium malaria*e [4].

Efforts to control malaria in South America, Southeast Asia and other regions have been complicated by increased *P. falciparum* resistance to former first-line antimalarial drugs chloroquine and sulfadoxine-pyrimethamine (S/P) [5]. This problem has fuelled renewed efforts to create alternative therapeutics for malarial treatment that are effective against blood stage parasites and are relatively non-toxic and affordable. Currently, the most effective drugs available are artemisinin-based combination (ACT) therapies, which combine an artemisinin derivative with a longer lasting partner drug.

Malaria parasites have been found to be associated with lipid peroxidation accompanying reduction in antioxidant capacity of the infected patients especially *Plasmodium falciparum* infection [6, 7]. In this study, a biomarker of lipid peroxidation, malondialdehyde will be evaluated in patients with *Plasmodium* malaria infection. Earlier research workers reported about increased lipid peroxidation in malaria patients, particularly *Plasmodium falciparum* infection [8]. Instantaneous reduction in

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antioxidant potency in tandem with increased lipid peroxidation is also observed to be equally accountable for the development of oxidative stress in malaria patients [9]. Any infection including malaria activates the immune system of the body thereby causing release of reactive oxygen species as antimicrobial action [10]. In addition to the host immune system, malaria parasite also stimulates certain cells in the production of reactive oxygen species thereby resulting in hemoglobin degradation [11].

It has been documented by several researchers, Bhattacharyya, *et al*. [12], Ittarat, *et al*. [13], Pan, *et al*. [14] that the mechanism of most antimalaria drugs involves the generation of free radicals which in turn helps to kill the malaria parasites. It is therefore the aim of this study to investigate the effects of antimalaria drugs on the antioxidant defense system of malaria patients.

MATERIALS AND METHODS

Subjects: The study population in this investigation comprised of 87 malaria parasite infected patients who attended Central Hospital, Benin-City and a private hospital, Time Hospital in Benin-City, Edo State, Nigeria. Apparently, thirteen (13) subjects who were found to be negative for *Plasmodium* paraiste in the peripheral blood were used as control. Inclusion criteria include, patients on the anti-malaria drugs, chloroquine, artemisinin-based combination (ACT) and sulfadoxine-pyrimethamine (Fansidar). Patients biodata (age, sex and social status) and the clinical history (duration of illness and drug used) were recorded. Laboratory investigations were carried out to determine the degree of parasitemia. The severity of malaria was defined according to the WHO criteria, mild + (1-999/µL), moderate ++ (1000-9999/µL) and severe +++ (>10, 000/µL. A total of 100 subjects (both male and female) including normal control were recruited for this study.

Ethical permission was obtained from Central Hospital and Time Hospital, Benin-City, Nigeria. The scope, nature and objectives of this investigation were thoroughly explained to the patients or their relatives for their consents.

Collection and Preparation of Samples: Blood samples were collected in 5ml EDTA and 5ml plain bottles from the patients and delivered to the laboratory within 3hrs after collection. The EDTA blood sample was used in the determination of the degree of parasitemia (using Giemsa stain). The plain bottle containing blood sample was used for biochemical assays. Serum was separated after standing for 10 minutes by centrifugation at 1500g for 10mins at 25°C and also the red blood cells were stored along side with the serum in refrigerator at -4°C for analytical purposes.

ASSAYS: *Plasmodium falciparum* parasitaemia was determined in peripheral blood smears stained with Giemsa stain. The thick and thin films were analysed for the number of parasites per 200 white blood cells. Slides were considered negative if no parasites were seen in 100 fields in the film.

Estimation of vitamin C was done by the method of Sadasivam and Manickam (1997) [15], while serum Vitamin E was estimated by the method of Baker and Frank (1968) [16].

Catalase activity was determined by the method of Cohen *et al*. [17], while superoxide dismutase activity was estimated by the method of Fridovich (1995) [18].

The activity of glutathione peroxidase was determined by the method of Addy and Goodman (1972) [19], a modification of the Chance and Meahly method (1955).

Lipid peroxidation was estimated in terms of thiobarbituric acid reactive species (TBARS), using malondialdehyde (MDA) as standard by the method of Buege and Aust (1978) [20].

Statistical Analysis: Data are presented as means ± SEM. Statistical analysis was performed by Duncan's Multiple Range Test (DMRT) using the SPSS version 16.0 computer program. P values less than 0.05 was considered significant and values with different superscript alphabets differ significantly ($p<0.05$). Correlation analysis and linear regression were also plotted.

RESULTS

Table 1 shows the antioxidant status of the malaria patients. The antioxidant molecules, vitamins C and E of the patients decreased significantly ($p<0.05$) compared to the control. The MDA level, which is a marker of the extent of lipid peroxidation increased significantly ($p<0.05$) in the patients compared to the control subjects. Antioxidant enzymes, catalase and peroxidase in the patients were significantly decreased ($p<0.05$) compared to their control counterparts. There were no significant changes in the superoxide dismutase activities of the patients compared to the control.

Table 1: Antioxidant and Oxidant Status of Malaria Patients

Analytes/ Subjects	Vitamin C (µg/l)	Vitamin E (µg/l)	MDA (µmol/ml)	SOD (U/mg)	Catalase (U/mg)	Peroxidase (U/mg)
Control	12.7±0.87[a]	27.72±1.46[a]	176.98±15.01[a]	3.70±0.12[a]	17.53±2.21[a]	15.00±1.05[a]
Patients	8.96±0.27[b]	18.96±0.59[b]	577.55±20.06[b]	2.79±0.06[a]	11.08±0.43[b]	8.92±0.25[b]

Values represent mean ± SEM

KEY: MDA = malondialdehyde, SOD = superoxide dismutase

Table 2: Effect of Degree of Parasiteamia on Antioxidant Status of Malaria Patients

Degree of Parasiteamia/Analytes	Vitamin C (µg/l)	Vitamin E (µg/l)	MDA (µmol/ml)	SOD (U/mg)	Catalase (U/mg)	Peroxidase (U/mg)
Control	12.70±0.87[a]	27.72±1.46[a]	176.98±15.00[a]	3.70±0.12[a]	16.76 ±1.90[a]	14.97±1.05[a]
Mild (+)	9.47±0.30[b]	18.16±0.34b	503.80±15.03[b]	2.98±0.05[b]	12.63 ± 0.42[b]	10.90±1.13[a]
Moderate (++)	5.54±0.48[c]	14.66±0.54[c]	728.53±39.76[c]	2.23±0.07[b]	8.93±0.78[c]	7.13±0.28[b]
Severe (+++)	4.417±2.27[c]	7.77±2.45[d]	877.50±73.81[c]	1.70±0.31[c]	6.88±0.87[c]	4.09±0.47[b]

Values represent mean ± SEM

Table 3: Effect of Duration of Illness on Antioxidant Status of Malaria Patients

Duration of illness/Analytes	Vitamin C (µg/l)	Vitamin E (µg/l)	MDA (µmol/ml)	SOD (U/mg)	Catalase (U/mg)	Peroxidase (U/mg)
Control	12.70±0.87[a]	27.72±1.46[a]	176.98±15.00[a]	3.70±0.12[a]	16.76±1.90[a]	14.97±1.05[a]
1-4 days	9.17±0.42[b]	19.98±0.65[b]	592.42±32.02[b]	2.82±0.10[b]	11.12±0.78[b]	8.64±0.39[b]
5-8 days	6.61±0.44[c]	18.14±0.54[c]	576.64±25.94[b]	2.87±0.08[b]	10.75±0.46[b]	8.09±0.44[b]
9-12 days	3.35±0.28[d]	15.90±1.34[c, d]	581.17±72.80[b]	2.57±0.17[b, c]	9.97±1.22[b]	7.57±0.66[b, c]
13 days and above	2.81±0.60[d]	13.98±1.04[d]	663.16±45.24[b]	2.31±0.14[c]	9.74±1.36[b]	6.61±0.65[c]

Values represent mean ± SEM

Table 4: Effect of Drug Administration on Antioxidant Status of Malaria Patients

Analytes/Drug	Vitamin C (µg/l)	Vitamin E (µg/l)	MDA (µmol/ml)	SOD (U/mg)	Catalase (U/mg)	Peroxidase (U/mg)
Control	12.70±0.87[a]	27.72±1.46[a]	176.98±15.01[a]	3.70±0.12[a]	16.76±1.09[a]	15.00±1.05[a]
ACT	9.71±0.62[b]	18.11±0.81[b]	534.48±26.78[b, d]	2.88±0.10[b]	12.85±0.83[b]	9.34±0.41[a, b]
CQ	9.89±1.53[b]	18.31±0.63[b]	675.60±44.32[c]	2.59±0.18[b]	10.08±1.17[b]	8.32±0.56[a, b]
Fansidar	7.77±1.23[b]	15.37±0.59[b]	609.43±31.14[b, c, d]	2.87±0.29[b]	8.34±1.34[b]	7.92±1.62[a, b]
No Drug	8.57±2.29[b]	16.59±0.56[b]	612.96±26.00[b, c]	2.74±0.08[b]	10.84±0.63[b]	10.18±1.47[b]
Others	9.39±1.93[b]	18.09±1.17[b]	505.07±44.68[d]	2.96±0.13[b]	11.30±0.82[b]	9.78±0.44[a, b]

Values represent mean ± SEM

KEY: ACT = Artemisinin combination therapy, CQ = chloroquine,

Table 5: Effect of Gender on Antioxidant Status of Malaria Patients

Analytes/ Gender	Vitamin C (µg/l)	Vitamin E (µg/l)	MDA (µmol/ml)	SOD (U/mg)	Catalase (U/mg)	Peroxidase (U/mg)
Male						
Control	13.11±0.80[a]	26.66±1.28[a]	181.55±19.95[a]	3.75±0.18[a]	16.83±2.32[a]	14.45±1.17[a]
Patients	7.71±0.37[b]	16.57±0.68[b]	614.16±24.76[b]	2.78±0.09[a]	10.91±0.67[b]	8.14±0.39[b]
Female						
Control	15.22±1.48[a]	29.40±3.39[a]	189.66±14.64[a]	3.61±0.12[a]	16.85±3.70[a]	15.79±2.13[a]
Patients	9.72±0.34[b]	18.07±0.77[b]	570.88±25.69[b]	2.81±0.08[b]	11.15±0.56[b]	9.34±0.37[b]

Values represent mean ± SEM

Table 6: Effect of Age on Antioxidant Status of Malaria Patients

Analytes/Age	Vitamin C (µg/l)	Vitamin E (µg/l)	MDA (µmol/ml)	SOD (U/mg)	Catalase (U/mg)	Peroxidase (U/mg)
Control	12.70±0.87[a]	27.72±1.46[a]	176.98±15.00[a]	3.70±0.12[a]	16.76±1.90[a]	15.00±1.05[a]
1-10 years	6.02±0.77[b]	14.36±1.58[b]	692.99±59.08[b]	2.12±0.18[b]	11.01±1.91[b]	6.63±0.61[b]
11-17years	8.43±0.80[b, c]	16.35±0.72[b, c]	588.10±89.10[c]	2.51±0.17[b, c]	11.46±1.57[b]	7.91±0.68[b, c]
18-30 years	8.73±0.31[c]	17.88±0.47[c]	593.62±23.20[c]	2.81±0.07[c]	10.96±0.51[b]	9.11±0.27[c]
31 years and above	9.08±0.42[c]	25.20±1.12[a]	559.12±32.39[c]	2.99±0.09[c]	11.06±0.82[b]	9.07±0.36[c]

Values represent mean ± SEM

Table 2 shows the effect of the degree of parasitaemia on antioxidant status of malaria the patients. The antioxidant molecules, vitamins C and E decreased significantly (P<0.05) with increase in the parasitaemia load compared to the control. The antioxidant enzymes SOD and catalase also decreased significantly (P<0.05) with the increase in the degree of parasitaemia compared to the control. Peroxidase activity were only significantly decreased (P<0.05) in patients with severe parasitaemia, while patients with mild and moderate showed no significant decrease compared to control. The MDA level of the patients increased significantly (P<0.05) compared to the control with increase in parasitaemia load.

Table 3 shows that vitamins C and E, SOD, catalase and peroxidase activities decreased significantly (P<0.05) compared to the control with increase in the duration of illness. However, MDA levels were significantly increased (p<0.05) in the patients with increase in the duration of illness when compared to the control subjects.

As shown in Table 4, there were no significant differences in the decrease in antioxidant status of the patients with respect to the drug used; although, they all decreased significantly (p<0.05) compared to the control. The MDA level of patients on CQ, ACT and fansidar showed the highest significant increase (P<0.05) respectively when compared to control patients. Patients on non antimalarial drug showed non-significant increase (p>0.05) in vitamin C and E, catalase and peroxidase and non-significant decrease (p>0.05) in MDA and SOD when compared to patients on anti-malarial drugs.

The vitamins C and E, SOD, catalase and peroxidase activities in both male and female patients decreased significantly (P<0.05) when compared to their respective control. The MDA of both male and female patients increased significantly compared (P<0.05) to control (Table 5).

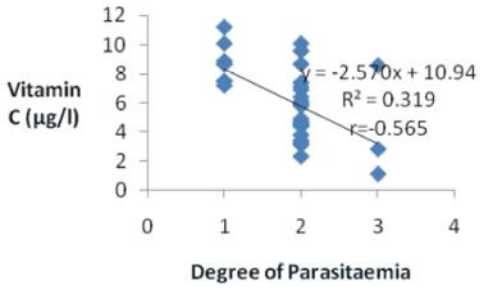

Fig. 1: Correlation between the degree of parasitaemia and vitamin C status of malaria patients (Negative correlation)

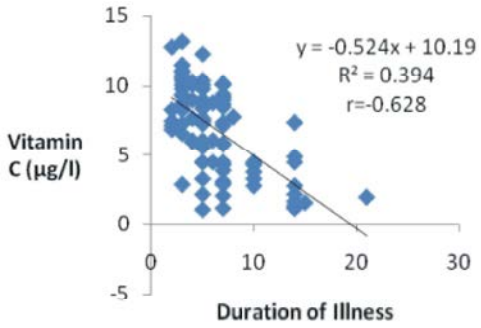

Fig. 2: Correlation between the duration of illness and the vitamin C status of malaria patients (Negative correlation)

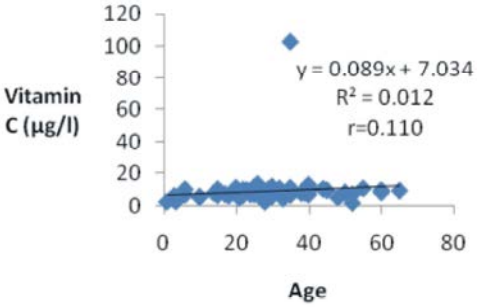

Fig. 3: Correlation between age and vitamin C status of malaria patients (Positive correlation)

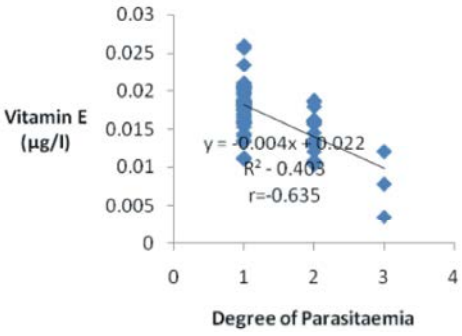

Fig. 4: Correlation between the degree of parasitaemia and Vitamin E level of malaria patients (Negative correlation)

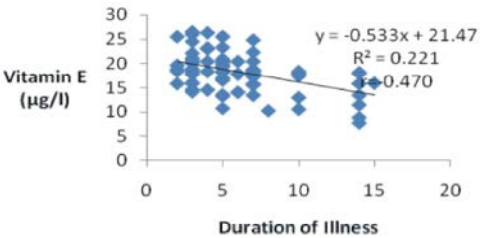

Fig. 5: Correlation between the duration of illness and Vitamin E level of malaria patients (Negative correlation)

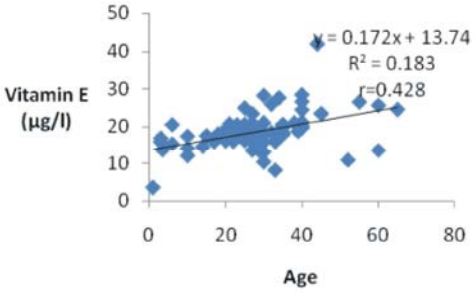

Fig. 6: Correlation between age and Vitamin E level of malaria patients (Positive correlation)

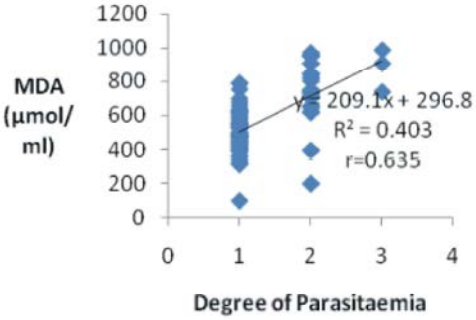

Fig. 7: Correlation between the degree of parasitaemia and the MDA level of malaria patients (Positive correlation)

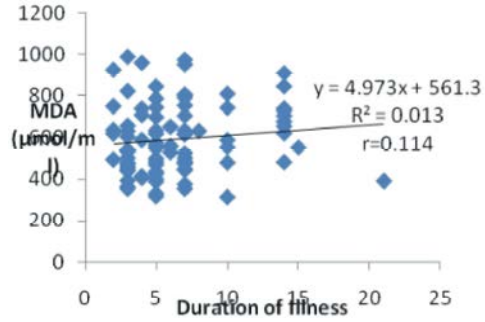

Fig. 8: Correlation between the duration of illness and the MDA level of malaria patients (Positive correlation)

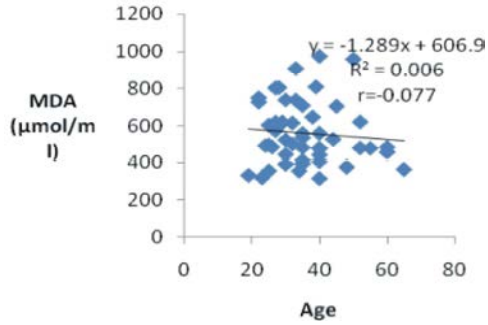

Fig. 9: Correlation between age and the malonydialdehyde level of malaria patients (Negative correlation)

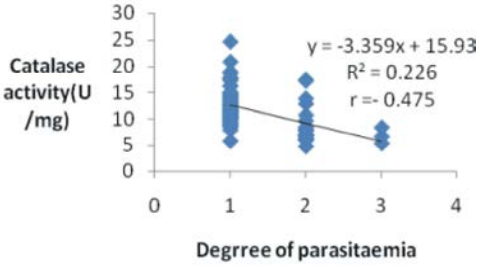

Fig. 10: Correlation chart between the degree of parasitaemia and catalase activity (Negative correlation)

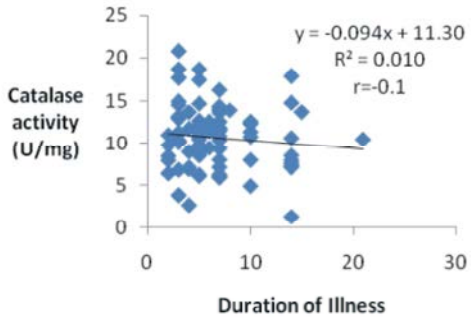

Fig. 11: Correlation between the duration of illness and catalase activity of malaria patients (Negative correlation)

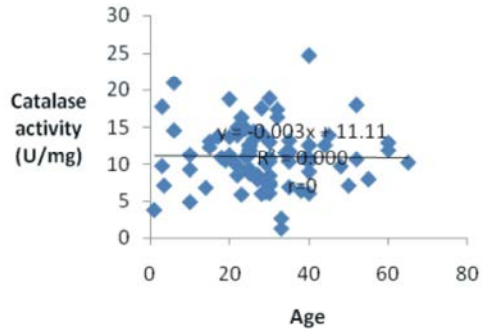

Fig. 12: Correlation between age and catalase activity of malaria patients (No correlation)

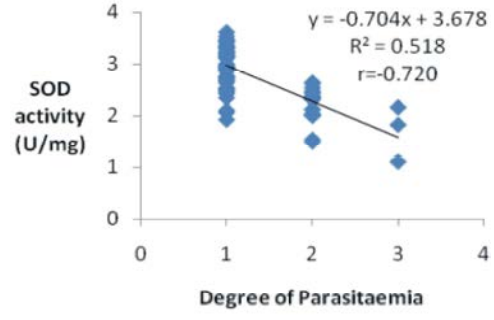

Fig. 13: Correlation between the degree of parasitaemia and superoxide dismutase activity of malaria patients (Negative correlation)

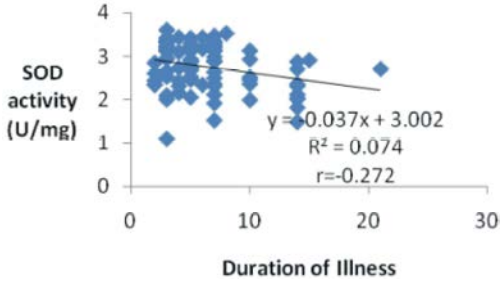

Fig. 14: Correlation between the duration of illness and superoxide dismutase activity of malaria patients (Negative correlation)

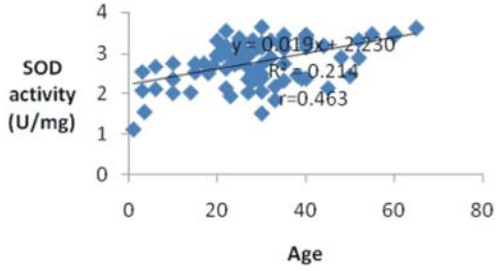

Fig. 15: Correlation between age and superoxide dismutase activity of malaria patients (Positive correlation)

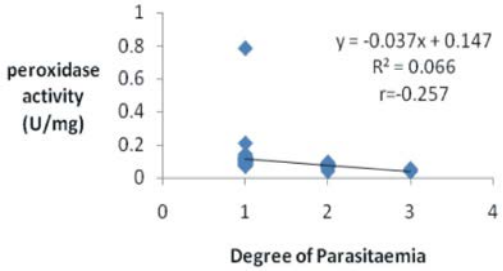

Fig. 16: Correlation between the degree of parasitaemia and guthathione peroxidase activity of malaria patients (Negative correlation)

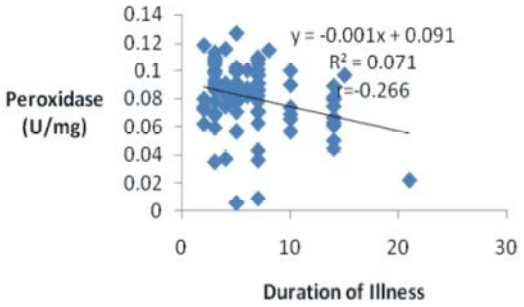

Fig. 17: Correlation between the duration of illness and glutathione peroxidase activity of malaria patients (Negative correlation)

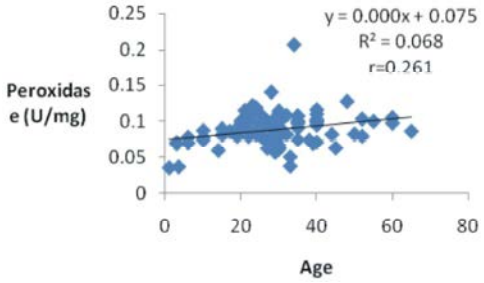

Fig. 18: Correlation between age and glutathione peroxidase activities of malaria patients (Positive correlation)

The antioxidant level of children (1-10 years) showed the greatest significant decrease ($P<0.05$) compared to the others. As the age decreases, the antioxidant enzymes' activities decrease. The MDA level also increased significantly ($P<0.05$) with decrease in age (Table 6).

The correlation analysis and linear regression of the analytes with respect to the various conditions are represented in Figures 1-18 and the respective relationships expressed.

DISCUSSION

Malaria infection has been found to be associated with lipid peroxidation accompanying reduction in antioxidant capacity of the infected patients especially *Plasmodium falciparum* infection. The highly elevated levels of MDA obtained in this study in malaria positive patients is an indication of increased production of reactive oxygen species. ROS are generated during the consumption of haemoglobin by the malaria parasite [21]. Increased production of H_2O_2 and O_2^- [22] and a decrease in antioxidant enzymes [23] have been observed in parasitized erythrocytes. A combination of reduced antioxidant enzyme defence and increased production of ROS leads to augmented oxidative stress as evidenced by high levels of lipid peroxidation products in malaria.

The antioxidant molecules, vitamins E and C levels were lower than the levels for the control with a significant increase in the level of MDA. The lower values observed in antioxidant vitamin levels in malaria may be attributed to increased utilization of the hosts serum antioxidants by malaria parasites to counteract oxidative damage [24]. It has been documented that antioxidants such as carotenoids and vitamins C and E could provide protection against oxidative stress induced by malaria [25]. The significant reduction in antioxidant enzymes

(Superoxide dismutase, catalase and glutathione peroxidase) of malaria patients compared to the control subjects might be as a result of the mobilization of these enzymes to counteract the oxidative stress produced by the malaria parasites and also that the parasite utilizes the host's antioxidant defense to counteract oxidative damage. Degradation of antioxidant enzymes by malaria parasite to produce its own protein has been reported by Koracevic *et al*. [26]. This might thus be contributing to the decline in total antioxidant status of malaria patients.

On the basis of the degree of parasitaemia (Table 2) and the negative correlations from the graph of vitamins C and E versus the degree of parasitaemia (Figures 1 and 4 respectively), there were significant decrease in the antioxidant status with increases in the parasite load. The positive correlation between the degree of parasitaemia and the MDA level of malaria patients (Figure 7) shows that the extent of lipid peroxidation (MDA) increases with increase in the parasitaemia load. Patients with moderate and severe malaria had significantly lower concentration of vitamins C and E than those with mild malaria and this suggests that these micronutrients may be utilized in the face of increased parasitaemia. This observation is in agreement with a previous investigation performed by [27], where they documented that both severe and moderate malaria had significant lower concentrations of vitamins E and C. Similarly, a negative correlation was obtained between the degree of parasitaemia and the antioxidant enzymes in malaria patients (Figures 10, 13 and 16), which indicated that at higher degree of parasitaemia, there is reduced activities of the antioxidant enzymes, thus lowering its level. Malaria parasite is sensitive to oxidative stress and the level of oxidative stress is influenced by the severity of the malaria infection [28 and 29], which agrees with this present study, where the level of MDA was significantly increased compared to the control.

Table 4 compares the antioxidant status of patients on drugs (chloroquine, athermisinin combination therapy and fasidar) and patients who did not use any anti-malaria drug to control subjects. The level of antioxidant molecules, vitamins C and E and antioxidant enzymes in patients on fansidar was significantly lower compared to all the other test groups; this is so because one of the observed adverse effects of fansidar and some antimalarials is the induction of oxidative stress by generating large quantities of reactive oxygen species [30]. Adisa *et al*. [30], investigated the effects of fansidar on cellular defense system and the extent of lipid peroxides in the blood. The study inferred that the treatment of rabbits with fansidar alters the antioxidant defense profile and induces oxidative stress in the body. However, there was increase is the activity of SOD compared to patients who did not take any antimalarial. This is similar to reported observations with chloroquine treatment [31, 32, 33 and 34]. The result shows that fansidar appears to affect the overall redox status of the cells in the blood as indicated by the alteration in the activity of glutathione peroxidase. This result is in agreement with the result of Bhattacharyya *et al*. [12]. There were reduction in SOD and catalase activities of patients on ACT compared to the control, but they were higher than in patients who did not use any drug. This is because the mechanism of action of ACT, an antimalarial containing endoperoxide, involves the generation of free radicals to kill the malaria parasite, thus leading to a reduction in the antioxidant enzymes compared to the control. This result is in line with the findings of previous researchers [35]. There were also decrease in the antioxidant molecules; this is in agreement with the findings of Bhattacharyya *et al*. [12]. There were also increases in the antioxidant status of patients on chloroquine compared to patients who did not use any drug. Furthermore, from the results of this investigation, patients on chloroquine had the highest level of MDA; this may the due to the fact that the mechanism of action of chloroquine involves heme degradation which might have resulted in the higher level of MDA in chloroquine treated patients. This is in line with the report of Farombi *et al*. [36]; and earlier reports of Onyeneke *et al*. [32]; Onyeneke 2000 [33]; Mba *et al*. [34], that chloroquine mediates oxidative stress. There were also significant increases in the level of MDA of patients on ACT compared to the control in this study. Many lines of evidence reveal that artemisinin generates free radicals to kill malaria parasites [28]. Sodium artesunate, markedly increased the level of active oxygen species and production of malondialdehyde in normal red blood cells and to a greater extent, in malaria infected red blood cells [14]. Certain active oxygen species generated and accumulated in such red blood cells infected with malaria might in turn kill the parasites. Sodium artesunate augmented intracellular superoxide anion (O_2^{2-}) and hydrogen peroxide (H_2O_2) production and this may partly account for its mechanism of action [14].

The result of this study shows that there is a significant decrease in the antioxidant status and increase in the MDA level of malaria patients compared to control

subjects with increase in the duration of illness (Table 3). This is also revealed by the negative correlation obtained between the duration of illness and the antioxidant status (enzyme and non-enzyme) and a positive correlation from the plot of MDA versus the duration of illness. This is so because as the duration of illness increases, more oxidative stress is produced and hence the increased degradation of antioxidant molecules and enzymes. This result is in agreement with the earlier reports of Anionye *et al*. [6].

On gender status of the patients (Table 5), the antioxidant status of female was higher than that of their male counterparts. This might be due to gender norms and values that influence biochemical indices. This is supported by Akanbi *et al*. [37] that the prevalence of *Plasmodium* infection was reportedly higher in males than in females and subsequently translates to other biochemical and physiological indices. Also, studies have shown that females have better immunity to parasitic diseases and this has been attributed to genetic and hormonal factors. The observed significant lower antioxidant status prevalence among males compared to females in this study might also be due to the possibility that males have lower resistance to malaria as the production of estrogen by females have been shown to augment anti-plasmodia immune responses [38], whereas, testosterone suppresses anti-plasmodia immune responses [39]. In our society, men have a greater occupational risk that might contribute to high severity of malaria infection in men compared to women [40].

Among the different age ranges, children (1-10) years had the lowest concentration of vitamins E and C compared to others and to the control (Table 6). Their level of MDA was also significantly higher. This is also explained with the positive correlation obtained from the plot of vitamins C and E versus the age of the patients (Figs. 3 and 6 respectively) showing that antioxidant status of the patients was lowest among the youngest group of patients. This agrees with the investigation of Nmorsi *et al*. [41] performed in Ekpoma, Edo state, Nigeria and Das *et al*. [27] where they documented that those children with malaria had significant lower plasma concentration of vitamin E than their control counterparts without malaria. This may also be in part due to increased utilization of serum antioxidant or increased destruction during malaria infection. Their transfer to the red blood cell membrane to counteract the increase oxidative stress during acute phase of malaria by inhibiting membrane lipid peroxidation may be a contributing factor Nmorsi *et al*. [41]. Furthermore, previous observations by Adediran *et al*. [42] have shown that under-fives are the most vulnerable age group for malaria. In this age range, it could be seen that children had much reduced antioxidant level, which may be the consequence of frequent malaria infection or of severity of malaria [6 and 24].

Conclusively, this study revealed that malaria infection induces oxidative stress with a concomitant depletion in the antioxidant defense system of malaria patients. Furthermore, anti-malarials used in malaria chemotherapy increases the oxidative stress of malaria patients, this is because the mechanism of action of most anti-malarials tend to generate free radicals that kills the malarial parasites.

It is therefore suggested that supplementation of anti-malarial drugs with antioxidants should be part of treatment plan for the management of malaria patients.

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