Assessment of Some Liver Enzymes and Bilirubin Levels among Malaria Infected Patients in Jalingo, Taraba State.

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Abstract: Although the routine diagnostic procedure of malaria does not involve assessing liver chemistry in the above disease, morbidity and mortality are mostly due to complications arising from long standing liver dysfunctions. This study investigated the biochemical indices of liver function in individuals infected with malaria and compared their results with healthy group (age and sex-matched).
200 patients (age:1- 50 years) were enrolled from a tertiary health institution in Jalingo, Taraba state Nigeria. A hundred age and sex matched apparently healthy individuals from the same geographical location were selected as control. Examination of a thick blood film stained with Giemsa was done to confirm the presence of *Plasmodium* in patients and its absence in controls. The *in vitro* determination of the plasma activities of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and plasma total and conjugated bilirubin was performed with Randox reagent using standard methods. Data obtained were statistically analyzed using Student's t-test and Spearman correlation where $P < 0.05$ was considered significant.
There was a positive relationship between the enzyme activities and the level of parasitaemia ($p<0.05$). Derangement in the AST (17.25± 6.74 IU/L), ALT (13.43± 3.78 IU/L), total bilirubin (19.91± 3.79 IU/L) and conjugated bilirubin (6.40± 2.38 IU/L) levels for the infected subjects were higher when compared with the controls AST: 9.67± 1.53 IU/L, ALT: 5.52± 1.09 IU/L, total bilirubin: 4.65± 0.25 IU/L and conjugated bilirubin: 2.78± 0.22 IU/L ($p< 0.05$). The serum level of ALP did not increase in both test and controls. There was no statistical difference in the derangement level in both male and female victims across all age groups ($p> 0.05$).
Abnormal biochemical indices of liver functions observed in malaria patients does not conclusively imply liver disease; it could be as a result of intravascular haemolysis.

Keywords:, Malaria, Bilirubin, Liver enzymes, *Plasmodium.*

INTRODUCTION

Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a group of single-celled microorganisms) belonging to the genus *Plasmodium*. This is mainly transmitted by the bite of infected female Anopheles mosquitoes (WHO, 2014). In humans, malaria is caused by five (5) species of the parasites, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and rarely *Plasmodium knowlesi* (Mueller *et al*., 2007). *P. faliparum* is the most common cause (about 80%) of all malaria cases. The attitude of the people in the community and lack of basic infrastructural facilities may be responsible for the rampant prevalence of malaria infections. Malaria can be transmitted by three (3) known ways; vector transmission, blood transfusion and congenital transmission (Onyesom and Onyemakonor, 2011). The risk of the disease can be reduced by preventing mosquito bites using mosquito nets and insect repellents, or with mosquito-control measures such as spraying insecticides and draining standing water (Caraballo, 2014). The parasite interferes with 3 major organs in the body, namely: the brain, kidney and the liver (Dzeing-Ella *et al*., 2010). The severe manifestations often present clinically as cerebral malaria, pulmonary oedema, acute kidney injury, hypoglycaemia, lactic acidosis, anaemia and liver involvement (White, 1996). Malaria has been implicated as one of the factors responsible for human renal and hepatic

dysfunction in malaria endemic countries (Mishra *et al*., 2003; Sharma *et al*., 2004; Ogbadoyi *et al*., 2009). WHO estimates that in 2010 there were 219 million cases of malaria resulting in 660,000 deaths (WHO, 2012). In Sub-Saharan Africa, maternal malaria infection figure up to 200,000 estimated infant deaths yearly (Hartman *et al*., 2010). According to the WHO and UNICEF, deaths attributable to malaria in 2015 were reduced by 60% from a 2000 estimate of 985,000, largely due to the widespread use of insecticide-treated nets and artemisinin-based combination therapies. Efforts at decreasing the disease in Africa since the turn of millennium have been partially effective, with rates of the disease dropping by an estimated forty percent (40%) on the continent (Bhatt *et al*., 2015).

The liver is an important organ involved during the hepatic stage of the malaria parasite's life cycle, where malaria sporozoites develop into merozoites. Liver dysfunction is a common complication that usually occurs in malaria infection. Some studies have reported a sudden increase in liver enzymes in malaria infected individuals as an indication of liver dysfunction (Jarike *et al*., 2002; Onyesom and Onyemakonor, 2011). This could be as a result of the invasion of liver cells by the sporozoite during malaria parasite life cycle (Onyesom, 2012).The changes caused in the hepatic cell by sporozoite can lead to the leakage of parenchymal and membranous enzymes of the liver into the circulatory system, which can be responsible for the increase in liver enzymes (Burtis and Ashwood, 2001). Liver is one of the important organs of the body. It plays a vital role for the proper function of the body. Liver enzyme tests are broadly defined as tests useful in the evaluation and treatment of patients with hepatic dysfunction. They also help to monitor therapy and assess prognosis. In clinical diagnosis, plasma activities of AST, ALT and ALP are useful diagnostic markers of liver diseases. As a result of high level of complications and death of children due to malaria infection, there is need to evaluate the extent of hepatic dysfunctions in malaria cases so that there will be proper management of malaria infection and its associated complications (Ogbadoyi and Tsado, 2009).

AST is abundant in the liver, cardiac muscle, skeletal muscle and erythrocytes, relative to ALT while bilirubin is a breakdown product of haemoglobin metabolism (Renze *et al*., 2008). ALP is a useful diagnostic marker of liver diseases. Raised plasma activities of AST and elevated plasma level of unconjugated bilirubin could be as a result of liver disease as well as haemolysis of red blood cells. This study was aimed to determine if there would be any increase in plasma activities of liver enzymes and plasma level of bilirubin in patients presenting with malaria and to compare the findings of these parameters with those from age- and sex- matched apparently healthy individuals.

Materials and Methods

The study was carried out in Jalingo Local Government Area of Taraba State and majority of the population include; Civil Servants, Traders, Transporters and Farmers. Jalingo Local Government Areas have tropical continental type of climate characterized by well- marked wet and dry season.

Subjects

200 malaria infected patients and 100 apparently healthy individuals (controls) were recruited which included both children and adult aged 1 to 50 years including males and females at Jalingo, Taraba state, Nigeria. During the period of the investigation, subjects were differentially diagnosed not to have superimposed infections or clinically significant renal and hepatic conditions.

Sample collection and analysis

Blood samples (5mL) were collected by venepuncture into EDTA and plain containers. A drop of the whole blood was used for microscopic examination of malaria parasite by thick blood film and was stained with 10% Giemsa solution. The sample in the plain container was spun to obtain serum for the determination of plasma activities of aspartate transaminase (AST), alanine

transaminase (ALT), alkaline phosphatase (ALP), as well as plasma bilirubin concentration. Randox Enzymatic Kit was used for the *in vitro* determination of the plasma activities of ALT and AST using the Colorimetric method of Reitman and Frankel. Randox Enzymatic Kit was used for the *in vitro* determination of plasma activities of ALP, using the Colorimetric method of Bessey *et al*. (1946). Plasma total and conjugated bilirubin concentrations were determined using the Jendrassik-Grof method (1938).

Statistical Analysis

Statistical analysis was done using the statistical package for Social Science (SPSS 23) for windows software. Comparative analysis of level of enzymes and bilirubin in malaria infected and control were tested using Student´s t-test ($p \leq 0.05$). A P value of ≤ 0.05 was taken as significant.

Results

Table 1 depicts the comparison of some liver enzymes: AST, ALT, ALP and Bilirubin (TB and CB) levels among malaria positive patient and control. All the controls (100) had normal levels for AST- 100(100%), ALT- 100(100%), ALP- 100(100%), TB- 100(100%) and CB- 100(100%) while there were variations in malaria positive patients which showed some derangement in the level of enzymes and bilirubin.

Out of the 200 malaria positive patients, AST (n= 134; 67.0%), ALT(n= 82; 41.0%), TB(n= 181; 90.5%) and CB(n= 176; 88.0%) showed deranged levels except ALP that recorded(n= 0; 0.0%) for deranged level. Statistical analysis showed that there was a significant difference in the levels of the enzymes (AST, ALT) and bilirubin(TB, CB) among malaria positive patients and control ($P< 0.05$).

TABLE 1: Comparison of AST, ALT, ALP and Bilirubin (TB and CB) levels among malaria positive patients and controls in Jalingo ,Taraba State.

Parameters	Malaria Positive (%) N = 200		Control (%) N = 100		P Value
	Normal	**Deranged**	**Normal**	**Deranged**	
AST	66 (33.0%)	134 (67.0%)	100 (100%)	0 (0.0%)	0.000*
ALT	118 (59.0%)	82 (41.0%)	100 (100%)	0 (0.0%)	0.006*
ALP	200 (100%)	0 (0.0%)	100 (100%)	0 (0.0%)	
TB	19 (9.5%)	181 (90.5%)	100 (100%)	0 (0.0%)	0.012*
CB	24 (12.0%)	176 (88.0%)	100 (100%)	0 (0.0%)	0.013*

*= significant, N= number examined.

Table 2a compares enzymes and bilirubin levels among male control and male malaria positive patients.

All the male control (n= 57; 100%) each recorded normal levels for AST, ALT, TB and CB while there was no record (n= 0; 0%) of deranged level for the enzymes (AST and ALT) and bilirubin (TB and CB).

Out of 104 malaria positive males patients, (n= 27, 26%) were normal and (n=77; 74.0%) deranged. For AST, (n= 31; 29.8%) were normal and (n=73; 70.2%) deranged for ALT, while TB and CB recorded (n= 11; 10.6%) for normal and deranged (n= 93; 89.4%) each respectively. There were variations in the deranged levels of enzyme and bilirubin recorded for male patients

positive with malaria. The statistical analysis showed that there was a significant difference in levels of enzymes and bilirubin among the male control and that of their malaria positive counterparts (P< 0.05).

Table 2b compares enzymes and bilirubin levels among female control and female malaria positive patients.
All the female control (n=43; 100%) each recorded normal levels for AST, ALT, TB and CB while there was no record (n= 0; 0%) of deranged level for the enzymes (AST and ALT) and bilirubin (TB and CB). There were variations in the deranged levels of enzymes and that of bilirubin as recorded for the female malaria positive patients. Out of 96 females malaria positive patients,(n= 39; 40.6%) were normal and (n= 57; 59.4%) deranged for AST, (n= 65; 67.7%)were normal and (n= 31; 32.3%) deranged for ALT, (n= 8; 8.3%) were normal and (n= 88; 91.7%) deranged for TB and (n= 13; 13.5%) were normal while (n= 83; 86.5%) showed deranged levels for CB. The statistical analysis showed that there was a significant difference in the level of enzymes and bilirubin among female control and female malaria positive patients (P< 0.05).

TABLE 2a: Comparison of the levels of Enzymes and Bilirubin among male control and male malaria infected patients Jalingo, Taraba State.

Parameters	Control N= 57		Malaria Positive N= 104		P – value
	Normal	Deranged	Normal	Deranged	
AST	57 (100%)	0 (0%)	27 (26.0%)	77 (74.0%)	0.000*
ALT	57 (100%)	0 (0%)	31 (29.8%)	73 (70.2%)	0.004*
TB	57 (100%)	0 (0%)	11 (10.6%)	93 (89.4%)	0.010*
CB	57 (100%)	0 (0%)	11 (10.6%)	93 (89.4%)	0.012*

*= significant.

TABLE 2b: Comparison of levels of enzymes and bilirubin among female control and female malaria infected patients in Jalingo, Taraba State.

Parameters	Control N= 43		Malaria Positive N= 96		P – value
	Normal	Deranged	Normal	Deranged	
AST	43 (100%)	0 (0%)	39 (40.6%)	57 (59.4%)	0.001*
ALT	43 (100%)	0 (0%)	65 (67.7%)	31 (32.3%)	0.003*
TB	43(100%)	0 (0%)	8 (8.3%)	88 (91.7%)	0.002*
CB	43(100%)	0 (0%)	13 (13.5%)	83 (86.5%)	0.012*

*= significant

Table 2c compares enzymes and bilirubin levels among male and female malaria positive patients.
Out of 104 males, AST recorded (n= 27; 26%) as normal and (n= 77; 74%) as deranged, ALT recorded (n= 53; 51%) as normal and (n= 51; 49%) as deranged. TB and CB recorded normal (n= 11; 10.6%) and deranged (n= 93; 89.4%) each respectively.
96 females were examined out of which (n=39; 40.6%) were normal and (n=57; 59.4%) were deranged for AST; (n=65; 67.7%) normal and (n=31; 32.3%) deranged for ALT; (n= 8; 8.3%) normal and (n=88; 91.7%) deranged for TB; (n=13; 13.5%) normal and (n=83; 86.5%) were deranged for CB. Statistical analysis showed that there was no significant difference between male and female with regards to changes in enzymes and bilirubin levels among malaria positive patients (P> 0.05).

TABLE 2c: Comparison of levels of enzymes and bilirubin among male and female malaria positive patients in Jalingo, Taraba State.

Gender	Number examined	AST		ALT		TB		CB	
		Normal	Deranged	Normal	Deranged	Normal	Deranged	Normal	Deranged
Male	104	27(26%)	77 (74%)	53(51%)	51(49%)	11 (10.6%)	93(89.4%)	11 (10.6%)	93(89.4%)
Female	96	39(40.6%)	57(59.4%)	65(67.7%)	31(32.3%)	8 (8.3%)	88(91.7%)	13(13.5%)	83(86.5%)
Total	200	66	134	118	82	19	181	24	176
P value		0.101		0.101		0.769		0.302	

DISCUSSION

Analysis of some biochemical parameters are important instruments in disease detection, prompt diagnosis and intervention especially in endemic diseases like malaria.

The result showed a significant difference ($P < 0.05$) between the levels of AST, ALT and Bilirubin (Total and Conjugated) in malaria infected patients when compared with the non malaria infected (control) group. The increase in the serum levels of the transaminases (AST and ALT) especially in the severe (+++) malaria infected patients when compared with the non infected malaria control patients in this study showed that malaria parasite infection may be responsible for the increase in the liver enzymes and bilirubin levels. In this study, the observed derangement in AST and ALT levels could be attributed to the destruction of erythrocytes during the induced intravascular haemolysis of parasitized red cells and haemolysis of non-parasitized red cells by the erythrocytic stage of the *Plasmodium* parasite where merozoites caused the destruction of the infected red blood cells prior to their differentiations into male and female gametocytes leading to significant alterations in host cell physiology and morphology. Most of the mild (+) and moderately (++) malaria infected patients were not affected as regards to their enzyme levels. These transaminases (AST and ALT) are marker enzymes for liver toxicity especially ALT which is more specific to the liver. The liver being the major site of drug metabolism, most of the patients on anti malaria drugs or any forms of medication were excluded as higher increase in the level of these enzymes can result due to anti malaria drugs or any other medication as reported by Ogbadoyi and Tsado (2009). Elevated aminotransferases (AST and ALT) levels are commonly associated with compromised hepatic integrity where increase in ALT is far higher than AST while in intravascular haemolysis of the red blood cells, AST levels is higher than ALT as previously reported by Nsiah *et al*. (2011). Several studies stated more than five times (5x) increase in the level of all the serum liver enzymes in malaria patients which is an indication of liver damage (Anyasor and Olorunsogo, 2011; Onyesom and Onyemakonor, 2011). This present study however is inconsistence with the above fact as the increase in only AST and ALT levels observed were moderate especially in the severe (+++) malaria infected patients with more increase in AST than ALT. This finding is similar to the study conducted in Ondo by Olusegun (2015) who reported an increase in only AST and ALT level in severe malaria patients when compared with control groups. This could be due to induced intravascular haemolysis of parasitized red cells by *Plasmodium* and haemolysis of non-parasitized red cells by the erythrocytic stage of the parasite. This report is also in line with the previous studies done in India by Anurag *et al*. (2013) and Shikhare *et al*. (2017), who separately showed that *Plasmodium* infection may be responsible for the increase in the liver enzymes (AST and ALT).

In a study done by Uzuegbu *et al*. (2010) in Lagos State South West Nigeria on liver function test markers assayed in 230 patients, age range: 0-50 years, presenting with malaria infection, it was observed that the values for liver function profiles AST,

ALT and ALP among patients with the malaria were elevated when compared with those without infection. Also previous studies done by Anand *et al*. (1992) and Kausar *et al*. (2010), have documented liver dysfunction in *Plasmodium* malaria infection with increase in all the three enzymes (AST, ALT and ALP). They stated that the increase in these liver enzymes in malaria positive patients could be due to leakage of these enzymes from the liver as a result of damages to liver cell during the hepatic or liver stage of the life cycle of the malaria parasite. This study however is in contrast with Shikhare *et al*. (2017), who stated that the impairment of hepatic function is common in severe malaria. Acute malaria also badly affects the function of cytochrome P450 microsomal enzymes which is involved in detoxification reaction.

The ALP level were slightly higher in the control non infected group than in the severe and mild groups but it was not significant as both the levels in malaria infected patients and the non malaria infected control groups were still within the normal range. Deranged level of ALP is most commonly caused by liver diseases such as cholestasis, cirrhosis and bone disorders. ALP is present in the white blood cells and the observed increase in AST and ALT in this study could be attributed to the destruction of erythrocytes. During the induced intravascular haemolysis of parasitized red cells and haemolysis of non-parasitized red cells which did not affect the level of ALP as this enzyme is not affected by haemolysis which is in line with the studies of Lippi *et. al*. (2006) and Mehmet *et. al*. (2011) who reported a normal level of ALP in both in vivo and in vitro haemolysis.

In this study, the derangement in the level of bilirubin both Total and Conjugated in malaria infected patients were 90.5% and 88% respectively which showed a significant difference ($P< 0.05$) when compared with the non malaria infected (control) group. This increase in the level of Total and Conjugated bilirubin among malaria infected patients may be due to intravascular haemolysis which might have been caused by the destruction of the infected red blood cells at the erythrocytic stage by the merozoites prior to their differentiation into male and female gametocytes leading to significant alterations in host cell physiology and morphology. This is supported by the work of Sharma *et al*. (2012) and Whitten *et al*. (2010), who stated that the cause of elevated bilirubin is due to intravascular hemolysis caused by the destruction of infected red blood cells by merozoites. It is also in line with the work of Anand and Puri (2005), who reported that hepatic dysfunction in malaria infection, does not appear to be due to direct inflammation of hepatocytes but due to failure of bilirubin excretion in the liver which have accumulated due to increased destruction of red blood cells when the parasite densityis high. This is so since large numbers of erythrocytes are infected and they are eventually destroyed by the spleen. The resulting haemolytic anaemia from this destruction also lead to increased plasma level of bilirubin without any significant elevation of the liver enzymes.

A similar observation has been made by Abro *et al*. (2009) who noted that usually rise in bilirubin TB and CB in malarial infection is mainly due to hemolysis of parasitized and non parasitized red blood cells.

Gender as determinant in levels of enzyme / bilirubin among malaria positive patients. In this study, out of the 200 malaria infected patients, 52% were males and 48% females. This could be due to the fact that males expose themselves more than females to infected mosquitoes with *Plasmodium* especially during the hot weather. At such times, they tend to move about bare-bodied and expose themselves more to mosquito bites than the females. The derangement in enzyme levels and bilirubin were also significantly higher in malaria infected males and females as compared to their respective controls ($p<0.05$). There was however no significant difference ($p>0.05$) in the enzyme activities in both male and female malaria patients which showed that the effect of malaria infection on the enzymes was not gender specific. As soon as the parasite invades the body its pathogenesis sets in irrespective of sex and this is independent of the infection rate. This agrees with the previous study of Uzoegwu and Onourah (2003), who reported 51.1% in males and 41.4% in females in their work on malaria infected patients. Dhariyal *et. al*. (2016) also reported (62.5%) males against (37.5%) females out of total of 80 malaria positive patients. They all reported that derangement in enzymes and bilirubin were non gender specific. Therefore sex does not determine the level of these parameters in the malaria infected patients. This study disagrees with the reports of Ignatius *et al*. (2008) and Onyesom and Onyemakonor

(2011) who stated that males were affected more than females. It is probable that in this part of Nigeria were the current study was conducted; the degree of exposure of males and females may be the same to infected mosquitoes.

Conclusion

Malaria is a disease whose pathogenesis comes in different ways without any specific clinical presentation. The findings of this study revealed that the derangement in the levels of serum AST, ALT and bilirubin (Total and Conjugated) observed in malaria positive patients does not conclusively imply liver disease. This could be as a result of *Plasmodium* induced intravascular haemolysis. It is also important that liver enzymes and bilirubin be assessed and impairment properly managed in the course of malaria treatment to prevent complications and also post treatment analysis of these enzymes for comparison to fully clarify the involvement of liver in malaria infections.

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