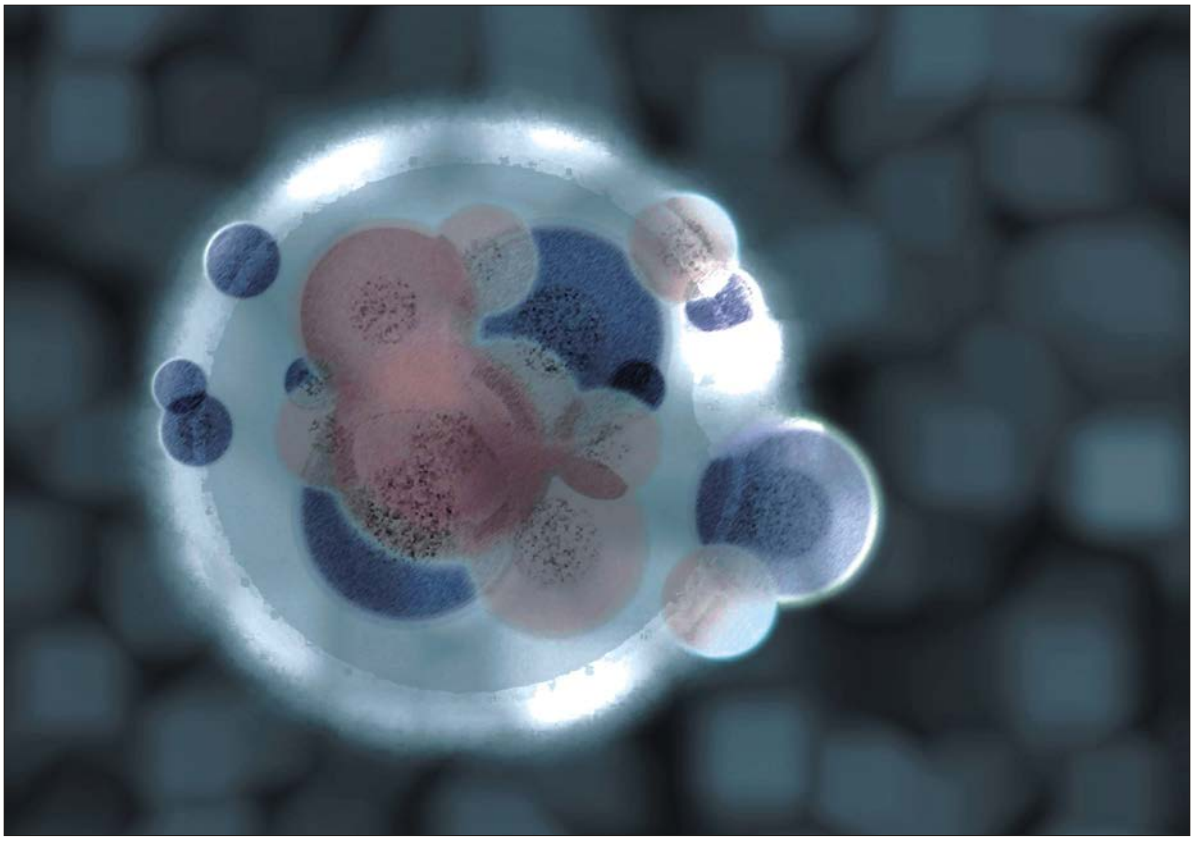

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Status of Selected Hematological and Biochemical Parameters in Malaria and Malaria-typhoid Co-infection

O.T. Kayode, A.A.A. Kayode and O.O. Awonuga
Biochemistry Unit, Department of Chemical Sciences, College of Natural and Applied Sciences,
Bells University of Technology, Km 8 Idiroko Road, P.M.B. 1015 Ota, Ogun State, Nigeria

Abstract: There has been high incidence of malaria and typhoid co-infection in Nigeria lately but no documented study has really considered its impact on the biochemical status of the patients. The aim of this study was to investigate the effect of malaria and malaria-typhoid co-infection on some hematological and biochemical parameters in infected patients. A total of 66 febrile patients and 10 apparently healthy persons from Bells University of Technology and Covenant University Health Centers, Ota, Ogun State were screened for the presence of *plasmodium falciparum* and *salmonella typhi*. Levels of Neutrophils, Lymphocytes, White Blood Cells, Packed Cell Volume (PCV), Albumin, Urea, Glucose, Total Bilirubin, Total Protein and Creatinine were estimated in the blood plasma of the study groups. A significant increase ($p<0.05$) in Creatinine, Urea and Total Bilirubin levels, Neutrophils and White Blood Cell counts were observed in both the malaria and co-infected patients as compared to the control. However, Albumin, Glucose, PCV, Lymphocytes and Total Protein levels were significantly reduced ($p<0.05$) in both the malaria and co-infected patients. This study indicates alterations in these parameters and therefore recommends proper monitoring during treatment in order to reverse them to normal levels.

Key words: Alterations, febrile, depleted, typhomalaria, apparently healthy, Ota

INTRODUCTION

Malaria which is the most prevalent infectious disease in the tropical and subtropical regions of the world is of great public health importance (Mishra *et al*., 2003; Umar *et al*., 2007; Mia *et al*., 2011). The World Health Organization reports that malaria, the deadly parasitic disease is responsible for nearly ninety percent of death in Africa (Ogbodo *et al*., 2010). One-fifth of infants' death in Africa is caused by the scourge of malaria (Snow *et al*., 2005; WHO, 2010). In Nigeria, approximately 0.25 million deaths of children under the age of five is caused by malaria yearly (UNICEF, 2009). Typhoid fever which is also endemic in Africa is more severe in infants and the elderly (Preston and Boreszyk, 1994; Gatsing *et al*., 2006). Both malaria and typhoid exhibit close symptomatology and epidemiology (Nsutebu and Ndumbe, 2001; Brian and Wahinuddin, 2006). The first case of malaria-typhoid co-infection occurred among American soldiers in 1862 (Bynum, 2002). The high incidence and prevalence of malaria-typhoid co-infection became popular almost ten years ago whereas the fact that malaria has been prevalently high is already recognized and accepted (Uneke, 2008). The onset and progression of the malaria infection is characterized by vast alterations in hematological and biochemical parameters (Bidaki and Dalimi, 2003). The World health Organization's (WHO) criteria acknowledges that some biochemical and hematological features should raise the severity of malaria (World Health Organization, 2000).

In different parts of the world including Nigeria, scientific materials on hematological and biochemical alterations in acute falciparum malaria are available (Mishra *et al*., 2003; Egwunyenga *et al*., 2004; Bidaki and Dalimi, 2003; Udosen, 2003), but none have really been reported from Sango-Ota, Ogun State, Nigeria and also scientific information on the impact of malaria-typhoid co-infection on hematological and biochemical parameters are scanty. This study examined the effect of malaria and malaria-typhoid co-infection on some hematological and biochemical indices. The study population includes only the febrile patients that have been clinically said to have malaria and malaria-typhoid co-infection from the results of their malaria and widal tests, respectively.

Corresponding Author: A.A.A. Kayode, Biochemistry Unit, Department of Chemical Sciences, College of Natural and Applied Sciences, Bells University of Technology, Km 8 Idiroko Road, P.M.B. 1015 Ota, Ogun State, Nigeria

MATERIALS AND METHODS

The study was conducted between September, 2010 and early June 2011. Inpatients and outpatients aged between 14 and 30 years with febrile illness in University Health Centers, Bells University of Technology and Covenant University, Ota, Ogun State, Nigeria. Necessary approval and consent were obtained from the appropriate authorities and individuals.

Experimental design and treatment: A total of 130 blood samples were collected from patients with a clinical suspicion of malaria and typhoid fever and screened for the presence of malaria parasites and *S. typhi* infection.

- **Group 1:** Patients with co-infection (36 patients)
- **Group 2:** Patients with malaria alone (30 patients)
- **Control group:** A total of 10 healthy individuals (from the same location with the febrile patients) were considered as a control group

Screening of blood samples to categorize the patients in the test group was done as follows:

- **Parasitological examination of blood samples:** Giemsa-stained thick and thin blood films was prepared for each sample and parasitaemia evaluated per microlitre of blood using the thick film preparation according to standard methods described by the World Health Organization (Gilles, 1991), assuming a leukocyte count of 5400 μL^{-1} of blood established for healthy Nigerians (Akinsanya and Grossman, 1973). Films were examined microscopically for the presence of malaria parasites within red blood cells in thin films. For thick films, the ring forms, trophozoites and gametocytes was looked for. A smear was considered negative for malaria parasites if no parasites are seen after examining at least 100 microscopic fields.

- **Widal test:** The Widal test was performed on all blood samples by the rapid slide titration method (Lynch and Raphael, 1983) using commercial antigen suspension for the somatic (O) and flagella (H) antigens. A positive widal test was considered for any given serum sample with antibody titer of 1:160 for *S. typhimurium* antigens
- Relationship between malaria parasite count μL^{-1} of blood and *Salmonella* O and H antibody titers was determined by carrying out a correlation analysis using the Microsoft Excel computer worksheet

Determination of White Blood Cell count (WBC): 0.95 mL of WBC diluting fluid was put into bijou bottle and blood sample was mixed by inverting approximately 20 times and 50 µL pipette was used to draw blood up into the tip. The content of the pipette was then expelled into the diluting fluid and the content of the bottle was mixed by inversion. The dilution of blood contained in the bottle was 1:20.

Determination of Packed Cell Volume (PCV): The blood was mixed by inverting about 20 times. Using a capillary pipette, the hematocrit was filled to the 10 mark, taking care to avoid bubbles. This was centrifuged at 3000 rpm for 30 min. The hematocrit was removed from the centrifuge and the height of the red cell column was noted. The height of the column of red cells was read off and expressed as a function of whole blood.

Determination of total bilirubin: The total bilirubin level in the plasma was assayed according to the method of Sherlock (1951) and as reported by Kazmierczack (1996a).

Determination of urea: Urea level in the plasma was determined according to the method described by Fawcett and Scott (1960).

Determination of albumin: Albumin concentration in the blood was estimated by the method of Doumas *et al.* (1971) and as described by Cheung and Hchman (1996).

Determination of glucose: Glucose level in the blood was assayed by the standard techniques reported by Kazmierczack (1996b).

Determination of creatinine: Creatinine level in the blood was determined according to the methods described by Bartels *et al.* (1972).

Determination of total protein: Briefly, 0.02 mL of the serum was placed in a cuvette containing 1.00 mL of reagent, R1 (Biuret reagent: Sodium hydroxide 100 mmol L^{-1}, Na-K-tartrate 16 mmol L^{-1}, Potassium iodide 15 mmol L^{-1}, Cupric sulphate 6 mmol L^{-1}). 0.02 mL of standard (Protein: 60 g L^{-1}) in another cuvette containing 1.00 mL of R1. Both preparations were mixed and incubated for 30 min at 25°C. The absorbance of the sample and of the standard was read at a wavelength of 546 nm against a reagent blank (Sodium hydroxide 100 mmol L^{-1}, Na-K-tartrate 16 mmol L^{-1}). Randox laboratories kits (Randox UK) were used for the entire biochemical assay.

Statistical analysis: All values were expressed as the Mean±SEM. Data were analyzed using Dennett's t-test (except for the Glucose and Total Protein in which the one away ANOVA method was used) using SPSS version 15.0 (SPSS Inc., Chicago, Il, USA). Values were considered statistically significant at $p<0.05$.

RESULTS

Table 1 shows the result obtained for the hematological parameters. It was observed that there was a significant decrease ($p<0.05$) in the lymphocytes level of the malaria and co-infected patients as compared to the control. The control group lymphocytes level 77.0±1.239 was depleted to 35.55±0.335 and 36.44±0.381 in the malaria and co-infected patients, respectively. Also, the malaria group shows a lower level compared to the co-infection group. However, a significant elevated neutrophils level was obtained in malaria (64.89±0.337) and co-infected (63.314±0.316) groups compared to the control (34.57±1.875). The malaria group shows a slightly greater increase in neutrophils than the co-infected groups. There was a significant increase ($p<0.05$) in the white blood cell count of the malaria and co-infected group as compared to the control. Co-infected group shows a lower WBC count compared to the malaria group. The data shows a significant decrease ($p<0.05$) in the packed cell volume of the malaria and co-infected groups. The malaria group PCV is lower compared to the co-infected group. Results obtained for the effect of malaria and co-infection on the biochemical parameters are depicted in Table 2. There was a significant decrease ($p<0.05$) in the albumin level of the malaria 7.018±0.098 g L^{-1} and the co-infection 6.307±0.071 g L^{-1} groups as compared to the control 13.838±1.162 g L^{-1}. The co-infection group has a significantly lower albumin level compared to the malaria group. We also observed a significant decrease ($p<0.05$) in the glucose level of the malaria 83.771±5.464 mg dL^{-1} and co-infection group 99.97±1.973 mg dL^{-1} compared to the control with the value of (115.394±10.669) mg dL^{-1}. However, there was a significant increase ($p<0.05$) in the urea level of the malaria 0.587±0.006 mmol L^{-1} and co-infection 0.539±0.007 mmol L^{-1} patients compared to the 0.329±0.022 mmol L^{-1} values in the control. Our data also reveals that malaria infection and the co-infection caused a significant increase ($p<0.05$) in the total bilirubin level when compared to the control. Statistically, there was no significant ($p>0.05$) difference in urea and total bilirubin levels between the malaria and the co-infection group. A significant increase ($p<0.05$) was obtained in the creatinine level of the malaria and co-infection patients. However, the co-infection group has a significantly lower creatinine level than the malaria group. The total protein concentration was significantly ($p<0.05$) reduced in the malaria group 46.01±6.91 g L^{-1} but significantly elevated in the co-infection group 65.14±6.45 g L^{-1} when compared to the control 61.25±5.00 g L^{-1}. This is illustrated in Table 3.

DISCUSSION

Alterations in biochemical and hematological parameters have been investigated and reported in malaria infections (Mishra *et al*., 2003; Udosen, 2003; Bidaki and Dalimi, 2003). It is necessary to include hematological and biochemical investigation in the diagnosis of malaria infection so as to detect early complications associated with acute malaria infection. This helps to intensively care for the patient and prevent death that may results from such complications. (Mishra and Mohanty, 2003). The result of this study shows that concurrent malaria-typhoid co-infection resulted in the alterations of some hematological and biochemical parameters. Packed cell volume was significantly reduced ($p<0.05$) in malaria and co-infected patients which can be as a result of increasing breakdown of red blood cells by the parasites, thus causing anaemia (Goselle *et al*., 2009). Ogbodo *et al*. (2010) reported reduced PCV levels in malaria patients.

Table 1: Effects of malaria and co-infection on hematological parameters as compared to the control

Parameters	Packed cell volume	White blood cell	Neutrophils	Lymphocytes
Malaria	35.96±0.358*#	6.537±0.085*	64.890±0.337*	35.55±0.335*
Co-infection	37.25±0.212*	6.520±0.069#	63.314±0.316#	36.44±0.381#
Control	44.70±0.632	5.110±0.227	34.570±1.875	77.00±1.239

*#Values are significantly greater than $p<0.05$. *Significantly different from control. #Significantly different from the co-infection group

Table 2: Effects of malaria Infection and co-infection on biochemical parameters as compared to the control

Parameters	Albumin (g L^{-1})	Urea (mmol L^{-1})	Glucose (mg dL^{-1})	Total bilirubin (mg dL^{-1})	Creatinine (mg dL^{-1})
Malaria	7.018±0.098	0.587±0.006	83.771±5.464	2.024±0.06	1.634±0.036
Co-infection	6.307±0.071	0.539±0.007	99.970±1.973	2.016±0.009	1.497±0.041
Control	13.838±1.162	0.329±0.022	115.394±10.669	1.810±0.003	1.285±0.106

Table 3: Results for total protein

Groups	Total protein (g L^{-1})
Co-Infection	65.14±6.45
Malaria	46.01±6.91
Control	61.25±5.00

Dangana *et al.* (2010) also reported decreased PCV levels in typhoid and paratyphoid patients which indicates that anemia might be involved. The findings in this study as regards PCV levels are consistent with the reports of the researchers mentioned above. The results of this study indicates significant increase ($p<0.05$) in the white blood cell count of the malaria and co-infected patients when compared to the control which can be as a result of increased secretion of the leukocytes at the onset of the infection to fight against the infection. Increase in WBC count in malaria patients has been reported by Sumbele *et al.* (2010). However, the works of Ali *et al.* (2009) reported both increased and decreased leukocytes counts in the blood of typhoid patients examined in Dubai.

Lymphocytes levels were significantly ($p<0.05$) depleted in the blood of the malaria and co-infected patients examined. This is in agreement with the work of Sumbele *et al.* (2010) which reported a decrease in the lymphocytes level of malaria patients in Cameroon. This study observes significant increase in the Neutrophils level of the co-infected and malaria patients when compared to the control. Ali *et al.* (2009) reported increase in Neutrophils level in typhoid patients. Dangana *et al.* (2010) also reported relative increase in typhoid patients in Abuja but it was not significant.

A significant ($p<0.05$) decrease was observed in the albumin level in both malaria and co-infected patients. This decrease is more pronounced in the co-infected patients, probably due to the combined infections. Malaria infections with its attendant pathology will decrease serum albumin at the onset. Albumin is synthesized in the liver hence, it is possible that initial inflammation of the liver may increase its production and there is influence in the production of the reactive protein especially in children. Also, symptoms of these infections associated with vomiting could have caused increased hemo-concentration and lead to initial increase in serum proteins. As the condition progresses, there is reduced liver functioning and increased adaptation to the condition including reduction in vomiting. At the same time, there will be continuous breakdown of the already produced albumin due to high fever and this causes reduction in serum protein especially albumin (Ogbodo *et al.*, 2010; Attwood, 2010). Ikekpeazu *et al.* (2010) also reported hypoalbuminaemia in patients with hepatitis-B surface antigen in malaria infection. Hence, malaria and malaria-typhoid infections affect the albumin level as shown by this study.

The data in this study indicates hypoglycemia in both the malaria and co-infected patients which can be observed when these infections are severe and can also be as a result of too little food or excessive secretion of insulin. Some researchers, for example, Adeosun *et al.* (2007), Attwood (2010) and Mazumder *et al.* (2009) have reported that reduced glucose level can also result during quinine administration especially to adults. In severe infections, quinine induces insulin and this may result in severe hypoglycemia which is accompanied with a great demand for glucose by the pathogens. Onyesom and Agho (2011) also reported hypoglycemia in malaria patients in Edo-Delta state.

Data presented in this study shows that plasma creatinine was significantly higher ($p<0.05$) in malaria and co-infected patients than in the control in Ota. The concurrent increase in serum creatinine level is mostly likely as a result of impaired glomerular filtration of urea and creatinine (Etim *et al.*, 2009) and that is also an indicator for acute malaria severity. Creatinine level can also increase temporarily as a result of muscle injury and are generally slightly lower during pregnancy. In some cases of infections such as malaria or co-infection, creatinine level can either be normal or high. Dialysis may be necessary in the management of hypercreatininaemia. Idonje *et al.* (2011), Adeosun *et al.* (2007) and Rajagopala *et al.* (2007) also reported high levels of creatinine in children and adults with malaria infection. High creatinine level has also been reported in disease and infections such as hepatitis, typhoid, urinary infections, kidney infections, diabetes which indicates acute renal failure.

This study reports hyperuricemia in the malaria and co-infected patients in Ota which can be attributed to increased catabolic rate which characterize the disease. This observation is supported by Ogbadoyi and Tsado (2009), who reported increased serum urea level in malaria patients in Minna. Etim *et al.* (2009) reported that increased Urea: Creatinine ratio in malaria patients also indicate that the causes of Uraemia in these patients are largely prerenal and may be due to reduced renal blood flow, rather than organic renal involvement. Reduced blood flow to the glomeruli due to malaria-associated hypotension may be responsible for the reduced glomerular filtration rate and hence decreased renal excretion of the analytes. Scragg, 1976 reported increased urea levels in children with typhoid fever. Idonje *et al.* (2011), Arinola *et al.* (2008), Monebenimp *et al.* (2010) and Uzuegbu (2011) reported increased urea levels in malaria in children, adults and also in sickle celled patients.

This finding reports significant increase ($p<0.05$) in the level of bilirubin in the malaria and co-infected patients in Ota. This findings correlates with the work of Adeosun *et al.* (2007), who reported elevated or hyperbilirubinaemia (Jaundice) in malaria and also typhoid fever patients which is a consequence of hemolysis but in severe infections can reflect liver damage. Attwood (2010), Mazumder *et al.* (2009), Paula and Christopher (2007) and Rajagopala *et al.* (2007) all reported presence of jaundice in cases of malaria, typhoid and some other disease causing infections. Etim *et al.* (2009) reported significantly raised bilirubin levels in untreated malaria patients. His finding suggests some degree of intravascular haemolysis of parasitized red blood cells in the malaria patients. Kochar *et al.* (2006) also reported elevated bilirubin levels in patients with malaria and acute viral hepatitis. Furthermore, this study showed significant ($p<0.05$) decrease in the concentration of total protein of malaria group. This coincides with many other earlier studies such as the work of Adekunle *et al.* (2007), Adebisi *et al.* (1998) and Adeosun *et al.* (2007) all of which reported significant decrease of plasma total proteins in malaria infections compared with non-infected control. The total protein in co-infected patients was found to increase ($p<0.05$) significantly compared with the control group. This finding showed that the values of total protein can be influenced by the degree of infection (Abdagalili and El-Bagir, 2009).

CONCLUSION

Severe malaria infection and malaria-typhoid co-infection caused significant alterations in hematologic and biochemical parameters, particularly those biochemical parameters relating to kidney functions.

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