Kidney Function Status in Nigerian Human Malaria Patients

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Abstract

Malaria is now known to affect over 500 million persons worldwide, killing about 1 to 3 million of them annually. Plasmodium falciparum is the species mostly implicated in the causation of severe malaria. This study was carried out to investigate the kidney function status of malaria patients in Benin metropolis, Southern Nigeria, to ascertain if there is renal dysfunction/impairment in them. Plasma levels of sodium, potassium, bicarbonate, urea, creatinine and blood urea nitrogen (BUN) were assayed in a total of 152 subjects (112 malaria patients infected with Plasmodium falciparum and 40 controls) of both sexes, with their age ranging from 8 to 42 years. The results observed irrespective of age or sex, reveal a statistically significant (p<0.05) increase in plasma levels of potassium, urea, BUN and creatinine (4.49±0.95 mmol/L;5.88±0.13mmol/L;16.39±0.36mg/dl and 135.05±2.69µmol/L) when compared to their controls (4.05±0.34mmol/L;3.73±0.12mmol/L;10.34±0.36mg/dl and 80.71±1.69µmol/L, respectively) and also a statistically significant (P<0.05) reduction in plasma levels of Na^+ and $HC0_3^-$ (128.50±0.77 and 19.98±0.28mmol/L) when compared to their controls (l38.58±0.29 and 24.70±0.36mmol/L, respectively). The hyponatraemia and metabolic acidosis observed in the malaria patients are negatively correlated with the degree of parasitaemia (r=-0.241 and r=-0.019, respectively), while the elevated plasma potassium and creatinine levels are positively correlated with the degree of parasitaemia (r=0.153 and r=0.407, respectively). The elevated plasma Urea and BUN levels are also positively correlated with the degree of parasitaemia (r=0.371 and r=0.375, respectively). The results of this study indicate that there is significant renal dysfunction/impairment in patients in southern Nigeria infected with plasmodium falciparum.

Keywords: Malaria infection, Kidney function status.

Introduction

Malaria is a life-threatening, mosquito-borne, parasitic, infectious disease caused by a eukaryotic protist of the genus *Plasmodium*, transmitted through the bite or the female anopheles mosquito (WHO, 2009). Five species of the plasmodium parasite can infect humans; the most serious forms of the disease are caused by *Plasmodium falciparum* (WHO, 2009). Each year, there are pproximately 350-500 million cases of malaria, killing between one and three million people, the majority of whom are young children in sub-Saharan Africa (Snow *et al*., 2005). Ninety percent of malaria-related deaths occur in sub-Saharan Africa. Malaria is commonly associated with poverty, and can indeed be a cause of poverty and a major hindrance to economic development (Snow *et al*., 2005; Sachs *et al*., 2002).

The pathophysiology of severe *Plasmodium falciparum* is characterized by anaemia, jaundice, liver failure, acute renal failure and sometimes death (Beare, et al., 2006). A common pathological change also observed in human and animal malaria is fatty infiltration in liver parenchyma cells which causes changes in the way the liver metabolizes certain metabolites (Fletcher and Maegraith, 1966). Severe organ damage has been reported in chronic cases and organs commonly affected include the gastro-intestinal tract, brain, liver, and the kidneys (Wernsdorfer and McGregor, 1988).

Research over the years has shown that the possible pathogenetic mechanisms are hyperparasitaemia with sequestration in

internal organs, intravascular haemolysis, Disseminated Intravascular Coagulopathy and immune and cytokine mediated injury (Bhattacharya and Manesh, 1998; Garg, 2000). Several factors including various chemical mediators, catecholamine release, cytoadherence of parasitized erythrocytes, dehydration, intravascular haemolysis, intravascular coagulation, sepsis, hyperbilirubinaemia and hyperparasitaemia, have been implicated in the pathogenesis of Acute Renal Failure (ARF) in malaria (Eiam-Ong and Sitprija, 1998; Mishra and Das, 2008). Acute tubular necrosis is the principal pathologic mechanism in malaria induced ARF (Eiam-Ong and Sitprija, 1998).

Recently, there is a changing trend not only in the clinical manifestations but also the pattern of complications in malaria. Over a decade ago, cerebral malaria was the predominant manifestation of severe malaria, whereas today the combination of jaundice and renal failure are more common (Nand *et al*., 2001). The hepatic and renal manifestations have been frequent and their mode of presentation has undergone a change making it difficult for the treating physician to differentiate these from other ailments. The renal involvement in malaria varies widely, from asymptomatic proteinuria to acute renal failure (ARF) (Boonpucknavig and Sitprija, 1979; Nand, *et al*., 1997). Reversible nephrotic syndrome is specifically associated with *P. malariae* infection (Claire *et al*., 2004).

Prevalence of Acute Renal Failure (ARF) in malaria all over the world has been reported as 0.57% to 60% (Mehta *et al*., 2001). In Southeast Asia there is an upsurge in the overall incidence of malarial ARF and has been reported to be between 13% and 17.8% (Mehta *et al.*, 2001). ARF occurs commonly in *Plasmodium falciparum* malaria, although its rare occurrence has been reported in *plasmodium vivax* malaria (Parkash *et al*., 2003). The disease is more common in adults in those areas of the tropics where transmission of malaria is low or unstable and where symptomatic disease occurs at all ages (WHO, 2000). Established ARF is usually oliguric, but urine output may also be normal or even increased in the presence of increasing serum creatinine values (WHO, 2000).

Depending on the degree of parasitaemia, the effect of *Plasmodium falciparum* on the kidneys and other organs is normally expressed in derangement in plasma electrolytes like a significant decrease in plasma sodium and elevation in plasma potassium (Alumanah *et al*., 1994) and many other metabolites which may be as a result of a dysfunction in the kidneys or liver (Onyeneke *et al*., 2003). These changes in many metabolites and the overall metabolism of the system(s) affected can sometimes result in death (Kreier, 1980; Ononogbu and Onyeneke, 1983; Alumanah *et al*., 1994).

In the last few years there has been a mass resurgence in malaria (Nand *et al*., 2001). Despite efforts to reduce transmission and increase treatment, there has been little change in areas which are at risk of this disease since 1992 (Hay *et al*., 2004). Indeed, if the prevalence of malaria stays on its present upwards course, the death rate could double in the next twenty years (Breman, 2001). Precise statistics are unknown because many cases occur in rural areas where people do not have access to hospitals or the means to afford health care. As a consequence, the majority of cases are undocumented (Breman, 2001).

Considering the endemicity of malaria in Nigeria and the mortality rate across families, accurate prognosis and proper management are very necessary. The incidence of kidney problems is on the increase in Nigeria, malaria and other infectious diseases may be contributing factors (Ogbadoyi and Gabi, 2007; Ekeanyanwu and Akpoilih, 2010). It is therefore important to know the prevalence level of renal involvement in malaria cases to ensure effective management of patients as they report to medical centres (Ogbadoyi and Gabi, 2007; Ekeanyanwu and Akpoilih, 2010). This is important because in the presence of acute renal failure, death increases three fold but with early detection and institution of frequent dialysis, mortality rate is reduced by 90% (Mishra *et al*., 2007).

Research regarding the effect of malaria on the kidneys, done in other parts of the world has been associated commonly with children under five years of age. So the impression in Southern Nigeria among adults more often than not is that kidney failure from malaria is a disease of Caucasians and ‘under-five’ children in Nigeria. Not much has been done comprehensively and in one single research in South-South Nigeria to understand the pathophysiology of malaria with respect to the kidneys.

The aim of this research is to determine the kidney function status of malaria patients in Benin metropolis, Southern Nigeria, It is the hope that any changes observed will not just aid the understanding of malaria pathogenesis in our environment but it will be applied to improve malaria diagnosis and

management as this will also bring to the consciousness of attending physicians, the need to not just prescribe appropriate doses of antimalarial drugs, but carry out routine renal function tests especially for those patients with severe infection and slow rate of recovery, with the intention of possible correction of any anomaly, especially those persisting after several days of treatment.

Materials and Methods

Study subjects: The study subjects were made up of a total of one hundred and forty (140) patients who reported ill with signs and symptoms suggestive of malaria and had not been placed on any anti-malaria drug. One hundred and twelve (112) of them (both sexes) were confirmed to have *Plasmodium falciparum* malaria and expressed symptoms ranging from fever (axillary temperature >37.5^{o}C), body/joint pain and headache to other clinical signs and symptoms of malaria as previously documented. The subjects who did not meet these criteria were excluded from the study. They were recruited from the General Out-Patient Departments of: the University of Benin Teaching Hospital, the University of Benin Health Centre, Ugbowo Campus, St. Philomena's Catholic Hospital, Dawson Road and Save Heavens Clinic all in the Benin Metropolis and transversing Oredo and Egor Local Government Areas of Edo State, South-South of Nigeria. The subjects were all Nigerians, resident in and around Benin City. They were divided into four different age ranges; 5-15. 16-25, 26-35, 36-45years.

Forty (40) apparently healthy age-matched individuals, who also did not test positive as carrying the malaria parasite were used as controls; though fifty (50) subjects were initially tested, only forty (40) of them were found suitable for use as controls. Informed consent was obtained from all the subjects and adequate approval was given by the personnel in charge in the health institutions before the study commenced.

Inclusion criteria: All the test subjects were confirmed to be infested with the malaria parasite. All control subjects were apparently healthy and had levels of the parameters being investigated within the normal range acceptable for Nigerians.

Exclusion criteria: Test subjects that did not test positive as carriers of the malaria parasite (even if this does not mean they did not have malaria) and control subjects that either tested positive as carriers of the malaria parasite or expressed symptoms of other diseases or abnormal levels of the parameters being investigated were excluded from this study.

Sample collection and preparation: two specimen bottles were used for each subject. Anticoagulant bottles containing dipotassium ethylenediaminetetraacetic acid (K_2 EDTA) for malaria parasite test and lithium heparin bottles for assay of other parameters were used for initial collection of blood from all subjects. Blood samples (5ml) were collected by clean venipuncture from the ante-cubital fossa of the subjects into already labeled bottles without undue pressure to either the arm or the plunger of the syringe. The samples were mixed by gentle inversion. The samples in the K_2 EDTA anticoagulant bottles were tested immediately for malaria parasite, after staining their thick films with Giemsa stain. Giemsa stained thin films confirmed the malaria parasite as purely *Plasmodium falciparum,* which is in keeping with the strain common in or endemic to Nigeria. The samples in the lithium heparin bottles were centrifuged at 4000r/min for 5mins to obtain plasma. The plasma were separated into sterile plain bottles and were used for assay of the required parameters; when immediate analysis was not possible, the samples were stored in the refrigerator (2–8^{o}C) and analysis carried out within 4 days.

Malaria parasite density determination: the malaria parasite density was determined by examining a thick blood film stained by Giemsa method (Cheesbrough, 1998).

Classification of the degree of parasitaemia: The malaria parasite density was graded as follows:

- 1 parasite/field: low density/ mild parasitaemia (+)
- 2-9 parasites/field: medium density/moderate parasitaemia (++)
- More than 20 parasites/field: high density/severe parasitaemia (+++) (Cheesbrough, 1998).

Determination of Plasma Sodium (Na^+) and Potassium (K^+): the plasma sodium and potassium levels were analyzed using flame emission spectrophotometric method (Flame Photometer) (Tietz *et al.*, 1996).

Determination of Plasma Bicarbonate (HCO_3^-): This was estimated following the first principle method (Titrimetric method) described by Davidson and Henry (1979)

Determination of Plasma Urea and Blood Urea Nitrogen (BUN): a urea Kit from Randox Laboratories Limited, UK (purchased from manufacturer's representative in Nigeria) was used. The assay method used, was that of Berthelot (Weatherburn, 1967). The Blood Urea Nitrogen was then determined using the formula:
BUN Concentration (mg/dl) = Urea Conc. (mmol/l) x 2.8 (Johnson *et al*., 1972).

Determination of Plasma Creatinine: a creatinine Kit from Randox Laboratories Limited, UK (purchased from manufacturer's representative in Nigeria) was used. The assay method used, was that described by Bartels and Bohmer (1972).

Statistical analysis: all the data from the study were statistically analyzed at 95% confidence interval. Some of the parameters were also investigated statistically for any correlation between them by determining their scatter plots and correlation coefficients. The analysis was done using the Statistics for Windows 16 version of Statistical Package for Social Sciences (SPSS - Windows 16). Results are presented as mean ± standard error of mean (SEM) and $p<0.05$ are considered significant.

Results

The Kidney function status of Nigerian Human Malaria patients from South-South Nigeria was investigated using some biochemical indices.

Table 1 shows some biochemical indices of the malaria patients. The mean age of the subjects used for the study did not differ significantly ($P>0.05$) while the other biochemical indices analyzed (Na^+, K^+, HCO_3^-, Urea, BUN, and Creatinine) for malaria subjects differ significantly ($P<0.05$) when compared to controls indicating that *P. falciparum* infection expressed significant reduction in plasma levels of Na^+ (hyponatraemia), HCO_3^- (metabolic acidosis), and significant elevation in plasma levels of K^+, Urea and BUN (azotaemia) and creatinine (hypercreatininaemia), in these patients.

Table 1: **Some biochemical indices of the malaria patients**

Parameters	Malaria Subjects	Control Subjects
Number of Subjects (N)	112.00	40.00
Age	24.49± 0.65[a]	23.10± 1.39[a]
Na^+ (mmol/L)	128.50± 0.77[a]	138.58± 0.29[b]
K^+ (mmol/L)	4.49± 0.95[a]	4.05 ± 0.34[b]
HCO_3^- (mmol/L)	19.98 ± 0.28[a]	24.70 ± 0.36[b]
Urea (mmol/L)	5.88 ± 0.13[a]	3.73 ± 0.124[b]
BUN (mg/dL)	16.39 ± 0.36[a]	10.34 ± 0.36[b]
Creatinine (µmol/L)	135.05 ± 2.69[a]	80.71 ± 1.69[b]

Results obtained also indicate that irrespective of the age of the patients, malaria infection universally caused a significant reduction ($P<0.05$) in the plasma levels of Na^+ (hyponatraemia) and HCO_3 (metabolic acidosis) and a significant elevation ($P<0.05$) in the plasma levels of K^+, Urea and BUN and creatinine (Table 2).

Table 2: Biochemical indices of malaria patients in relation to age

Parameters	Subject	N	5-15	N	16-25	N	26-35	N	36-45
Na^+ (mmol/L)	Malaria	4	127.00± 1.41[a]	75	129.03 ± 0.94[a]	26	128.12± 1.77[a]	7	125.14 ± 2.77[a]
	Control	7	138.57± 0.84[b]	22	136.68±0.397[b]	8	138.50±0.71[b]	3	138.00 ± 0.58[b]
K^+ (mmol/L)	Malaria	4	4.78±0.68[a]	75	4.41±0.11[a]	26	4.58±0.21[a]	7	4.90±0.37[a]
	Control	7	4.04±0.04[a]	22	4.00±0.42[b]	8	4.14±0.12[a]	3	4.17±0.03[a]
HCO_3^- (mmol/L)	Malaria	4	22.50±2.10[a]	75	20.20±0.05[a]	26	18.94±0.55[a]	7	20.00±0.82[a]
	Control	7	23.14±0.40[a]	22	25.7±0.03[b]	8	26.38±0.57[b]	3	26.00±1.53[b]
Urea (mmol/L)	Malaria	4	6.80±0.30[a]	75	5.80±0.14[a]	26	6.05±0.38[a]	7	5.61±0.45[a]
	Control	7	3.18±0.14[b]	22	3.71±0.169[b]	8	3.83±0.15[b]	3	4.83±0.68[a]
BUN (mg/dL)	Malaria	4	18.61±0.96[a]	75	16.22±0.40[a]	26	16.73±0.99[a]	7	15.70±1.27[a]
	Control	7	8.52 ± 0.41[b]	22	10.34 ± 0.05[b]	8	10.73 ± 0.42[b]	3	13.54 ± 1.91[a]
Creatinine (µmol/L)	Malaria	4	148.00±12.43[a]	75	131.90±3.06[a]	26	141.76±667[a]	7	137.00±10.93[a]
	Control	7	83.09±2.72[b]	22	82.19±2.59[b]	8	72.68±2.22[b]	3	85.67±3.82[b]

Values in the same box with different alphabets superscripts differ significantly ($P<0.05$)

Table 3: Comparison between biochemical parameters in the different age brackets of malaria subjects

Parameters	5-15 vs 16-25	5-15 vs 26-35	5-15 vs 36-45	16-25 vs 26-35	16-25 vs 36-45	26-35 vs 36-45
Na^+ N (mmol/L)	4 75 127.00±1.41[a] 129.03±0.94[a]	4 26 127.oo±1.41[a] 128.12±1.77[a]	4 7 127.00±1.41[a] 125.14±2.77[a]	75 26 129.03±0.94[a] 128.12±1.77[a]	75 7 129.03±0.94[a] 125.14±2.77[a]	26 7 128.12±1.77[a] 125.14±2.77[a]
K^+ N (mmol/L)	4 75 4.78±0.68[a] 4.41± 0.11[a]	4 26 4.78± 0.68[a] 4.58± 0.21[a]	4 7 4.78± 0.68[a] 4.90±0.37[a]	75 26 4.41± 0.11[a] 4.58± 0.21[a]	75 7 4.41± 0.11[a] 4.90± 0.37[a]	226 7 4.58± 0.21[a] 4.90± 0.37[a]
HCO_3^- N (mmol/L)	4 75 22.50±2.10[a] 20.20± 0.05[a]	4 26 22.50± 2.10[a] 18.94± 0.55[a]	4 7 22.50± 2.10[a] 20.00±0.82[a]	75 26 22.20± 0.05[a] 18.94± 0.55[a]	75 7 20.20± 0.05[a] 20.00± 0.82[a]	26 7 18.94± 0.55[a] 20.00± 0.82[a]
Urea N (mmol/L)	4 75 6.80±0.30[a] 5.80± 0.14[a]	4 26 6.80± 0.30[a] 6.05± 0.38[a]	4 7 6.80± 0.30[a] 5.61±0.45[a]	75 26 5.80± 0.14[a] 6.05± 0.38[a]	75 7 5.80± 0.14[a] 5.61± 0.45[a]	26 7 6.05± 0.38[a] 5.61± 0.45[a]
BUN N (mg/dL)	4 75 18.61±0.96[a] 16.22± 0.40[a]	4 26 18.61± 0.96[a] 16.73± 0.99[a]	4 7 18.61± 0.96[a] 15.70±1.27[a]	75 26 16.22± 0.40[a] 16.73± 0.99[a]	75 7 16.22± 0.40[a] 15.70± 1.27[a]	26 7 16.73± 0.99[a] 15.70± 1.27[a]
Creatinine N (umol/L)	4 75 148.0±12.43[a] 131.90± 3.06[a]	4 26 148.0± 12.43[a] 141.76± 6.67[a]	4 7 148.0±12.43[a] 137.0±10.9[a]	75 26 131.90± 3.06[a] 141.76± 6.67[a]	75 7 131.90± 3.06[a] 137.0± 10.9[a]	26 7 141.76± 6.67[a] 137.0±10.93[a]

Values in the same box with different alphabets superscripts differ significantly (P<0.05)

Table 4: Biochemical indices of malaria patients in relation to the degree of parasitaemia

Parameters	Subjects	N	(+)	N	(++)	N	(+++)
Na^+ N (mmol/L)	Malaria Control	70 40	129.69± 1.04[a] 138.58± 0.29[b]	25 40	128.36±1.23[a] 138.58± 0.29[b]	17 40	123.82± 1.67[a] 138.58±0.29[b]
K^+ N (mmol/L)	Malaria Control	70 40	4.37± 0.12[a] 4.05± 0.03[b]	25 40	4.66± 0.19[a] 4.05 ± 0.03[b]	17 40	4.77 ± 0.29[a] 4.05± 0.03[b]
HCO_3^- N (mmol/L)	Malaria Control	70 40	19.99± 0.32[a] 24.70± 0.36[b]	25 40	20.08± 0.56[a] 24.70± 0.36[b]	17 40	19.76± 1.00[a] 24.70± 0.36[b]
Urea N (mmol/L)	Malaria Control	70 40	5.53± 0.14[a] 3.73± 0.12[b]	25 40	6.08± 0.31[a] 3.73± 0.12[b]	17 40	7.00± 0.39[a] 3.73± 0.12[b]
BUN N (mg/dL)	Malaria Control	70 40	15.46± 0.38[a] 10.34± 0.36[b]	25 40	16.81± 0.79[a] 10.34± 0.36[b]	17 40	19.60+ 1.09[a] 10.34+ 0.36[b]
Creatinine N (umol/L)	Malaria Control	70 40	1.27± 2.86[a] 80.71± 1.69[b]	25 40	1.40± 4.87[a] 80.71± 1.69[b]	17 40	1.59± 8.85[a] 80.70± 1.69[b]

Values in the same box with different alphabets superscripts differ significantly (P<0.05)

Table 3 represents the comparison between biochemical parameters in the different age brackets of malaria patients. Generally there was no significant (P>0.05) mean difference in the parameters assayed in the malaria patients in the respective age groups when the values assayed for the respective age groups were compared with each other. Table 4 shows the biochemical indices of malaria patients in relation to the degree of parasitaemia. Results obtained indicate that irrespective of the degree of parasitaemia, malaria infection universally caused a significant reduction (P<0.05) in the levels of plasma Na^+ (hyponatraemia) and HCO_3^- (metabolic acidosis) and a significant elevation (P<0.05) in plasma levels of K^+, urea and BUN and creatinine, in these patients; and when compared to the different degrees of parasitaemia it was observed that there is a significant mean difference (P<0.05) in the plasma levels of sodium, potassium, urea, BUN and creatinine in the different levels of parasitaemia (Table 5). Table 6 represents the biochemical indices of malaria patients in relation to their sex. Results obtained indicate that though the levels of variation in the parameters assayed are generally higher in the males than in females, irrespective of the sex of the malaria patients, they both exhibit similar changes (P<0.05), like elevated levels of plasma potassium, urea, creatinine, BUN and reduced levels of plasma sodium and bicarbonate when compared with their corresponding male or female controls. When comparison between the biochemical indices in relation to their sex and degree of parasitaemia is made, the levels of variation in the biochemical indices assayed follow a similar pattern in the sexes but are generally higher in the males with increasing parasitaemia leading to elevated plasma potassium, urea, creatinine and BUN levels and hyponatraemia and metabolic acidosis, when compared with their corresponding male or female controls (Table 7).

Table 5: Comparison of biochemical parameters between the different degrees of parasitaemia in malaria subjects

Parameters	+ VS ++		+ VS +++		++ VS +++	
Na^+ N	70	25	70	17	25	17
(mmol/L) Value	129.70 ± 1.04[a]	128.36 ± 1.23[a]	129.69 ± 1.04[a]	123.82 ± 1.67[b]	128.36± 1.23[a]	123.82 ± 1.67[b]
K^+ N	70	25	70	17	25	17
(mmol/l) Value	4.37 ± 0.12[a]	4.66 ± 0..19[a]	4.37 ± 0.12[a]	4.77 ± 0.29[b]	4.66± 0.19[a]	4.77 ± 0.29[b]
HCO_3^- N	70	25	70	17	25	17
(mmol/l) value	20.00 ± 0.32[a]	20.08 ± 0..56[a]	20.00 ± 0.32[a]	19.76 ± 1.02[a]	20.08± 0.56[a]	19.76 ± 1.00[a]
Urea N	70	25	70	17	25	17
(mmol/l) Value	5.53 ± 0.14[a]	6.08 ± 0..31[a]	5.53 ± 0.14[a]	7.00 ± 0.39[b]	6.08± 0.31[a]	7.00 ± 0.39[a]
BUN N	70	25	70	17	25	17
(mg/dL) Value	15.46 ± 0.38[a]	16.81 ± 0..79[a]	15.46 ± 0.38[a]	19.60 ± 1.09[b]	16.81± 0.79[a]	19.60 ± 1.10[b]
Creatinine N	70	25	70	17	25	17
(µmol/l) Value	127.00 ± 2.86[a]	140.00 ± 4..87[a]	127.00 ± 2.86[a]	159.00 ± 8.85[b]	140.00± 4.87[a]	159.00 ± 8.85[b]

Values in the same block with different alphabets superscripts differ significantly (P<0.05)

Table 6: Biochemical indices of malaria patients in relation to their sex

Parameters	**Subjects**	**N**	**Male**	**N**	**Female**
Na^+ (mmol/L)	Malaria	32	129.16 ± 1.30[a]	80	128.24 ± 0.94[a]
	Control	21	138.14 ± 0.43[b]	19	139.05 ± 0.37[b]
K^+ (mmol/L)	Malaria	32	4.48 ± 0.18[a]	80	4.50 ± 0.11[a]
	Control	21	4.08 ± 0.06[b]	19	4.01 ± 0.4[b]
HCO_3^-(mmol/L)	Malaria	32	20.50 ± 0.46[a]	80	19.77 ± 0.34[a]
	Control	21	24.95 ± 0.51[b]	19	24.42 ± 0.49[b]
Urea (mmol/L)	Malaria	32	5.96 ± 0.25[a]	80	5.84 ± 0.16[a]
	Control	21	3.71 ± 0.13[b]	19	3.75 ± 0.22[b]
BUN(mg/dL)	Malaria	32	16.69 ± 0.71[a]	80	16.27 ± 0.42[a]
	Control	21	10.38 ± 0.36[b]	19	10.29 ± 0.67[b]
Creatinine (µmol/L)	Malaria	32	137.16 ± 5.45[a]	80	134 ± 3.10[a]
	Control	21	79.8 ± 2.69[b]	19	81.71 ± 2.01[b]

Values in the same box with different alphabets superscripts differ significantly (P<0.05)

Table 7: Comparison of biochemical indices of malaria patients in relation to their sex and degree of parasitaemia

Parameter	Subject	Mild Parasitaemia				Moderate Parasitaemia				Severe Parasitaemia			
		N	Male	N	Female	N	Male	N	Female	N	Male	N	Female
Na^+ (mmol/L)	Malaria	20	131.55±1.37^a	50	128.94± 1.33^a	7	126.14± 2.82^a	18	129.22± 1.31^a	5	123.80± 3.94^a	12	123.83± 1.85^a
	Control	21	138.14± 0.43^b	19	139.05± 0.37^b	21	138.14± 0.42^b	19	139.05± 0.37^b	21	138.14± 0.42^b	19	139.05± 0.37^b
K^+ (mmol/L)	Malaria	20	4.42±0.22^a	50	4.35± 0.14^a	7	4.31± 0.35^a	18	4.79± 0.22^a	5	4.98± 0.56^a	12	4.68± 0.34^a
	Control	21	4.08± 0.06^b	19	4.01± 0.04^b	21	4.08± 0.06^a	19	4.01± 0.04^b	21	4.08± 0.06^b	19	4.01± 0.04^b
HCO_3^- (mmol/L)	Malaria	20	20.70± 0.48^a	50	19.70± 0.40^b	7	19.57± 0.92^a	18	20.28± 0.69^a	5	21.00± 1.94^a	12	19.25± 1.18^a
	Control	21	24.95± 051^b	19	24.42± 0.49^a	21	24.95± 0.50^b	19	24.42± 0.49^b	21	24.95± 0.50^a	19	24.42± 0.50^a
Urea (mmol/L)	Malaria	20	5.44± 0.23^a	50	5.57± 0.171^a	7	6.16± 0.31^a	18	6.05± 0.42^a	5	7.76± 0.95^a	12	6.68± 0.38^a
	Control	21	3.17± 0.13^b	19	3..75± 0.22^b	21	3.71± 0.13^b	19	3.75± 0.22^b	21	3.71± 0.13^a	19	3.75± 0.22^b
BUN (mg/dL)	Malaria	20	15.23± 0.64^a	50	15.55± 0.47^a	7	17.24± 0.87^a	18	16.64± 1.05^a	5	21.74± 2.66^a	12	18.71± 1.06^a
	Control	21	10.29± 0.67^b	19	10.38± 0.67^b	21	10.38± 0.36^b	19	10.29± 0.67^b	21	10.38± 0.36^b	19	10.29± 0.67^b
Creatinine (µmol/L)	Malaria	20	126.69± 4.45^a	50	127.83± 3.60^a	7	136.80± 5.14^a	18	141.78± 6.51^a	5	180.75± 20.47^a	12	150.56± 8.58^a
	Control	21	79.81± 2.69^b	19	81.71± 2.01^b	21	79.81± 2.69^b	19	81.71± 2.01^b	21	81.71± 2.01^b	19	81.71± 2.01^b

Values in the same box with different alphabets superscripts differ significantly (P<0.05)

The hyponatraemia and metabolic acidosis (reduced plasma bicarbonate) observed in the malaria patients are negatively correlated with degree of parasitaemia (r=-0.241 and r=-0.019, respectively; Figures 1and 2, respectively). The elevated plasma potassium and plasma creatinine levels observed in the malaria patients, positively correlated with the degree of parasitaemia (r=0.153 and r=0.407, respectively; figures 3 and 4, respectively). The elevated plasma Urea and BUN levels observed in the malaria patients are positively correlated with the degree of parasitaemia (r=0.371 and r=0.375, respectively; Figures 5 and 6, respectively).

Discussion

Renal failure or kidney failure (formerly called renal insufficiency or chronic renal insufficiency) describes a medical condition in which the kidneys fail to adequately filter toxins and waste products from the blood (Evans, 1978). Biochemically, renal failure is typically detected by an elevated creatinine level in the blood and a decrease in the glomerular filtration rate (Evans, 1978). Problems frequently encountered in kidney malfunction include abnormal fluid levels in the body, deranged acid levels, abnormal levels of potassium, calcium, phosphate, haematuria (Blood in the urine) and (in the longer term) anaemia (Evans, 1978).

In this present study it was observed that there was a statistically significant (P<0.05) hyponatraemia in the malaria infected patients. The hyponatraemia was observed to be negatively correlated with the degree of parasitaemia and is experienced in the malaria patients irrespective of their age or sex. This result of significant hyponatraemia aligns with the results obtained earlier by Ikekpeazu *et al*., (2010), in South-East Nigeria. The result of this study also corroborates the earlier work by Van-Wolfswinkel *et al*. (2010), where a hyponatraemia in malaria patients which negatively correlated with the degree of parasitaemia was observed. The results of this study however differs from that of Ekeanyanwu and Akpoilih (2010) who earlier reported that hyponatraemia was not observed as there was no significant change in plasma Na^+ levels in the *Plasmodium* infected subjects compared to the controls. This study partly agrees with that of Ogbadoyi and Gabi (2007) who had shown a mean significant difference (P<0.05) in plasma sodium levels of all female categories of malaria patients and controls, but no significant difference (P>0.05) was found between the levels in male malaria patients and individuals without malaria.

Hyponatraemia (serum sodium< 135mmol/L) has long been recognized as a complication of malaria (English *et al*., 1996). In human erythrocytes infected with the mature form of the malaria parasite, *Plasmodium falciparum,* the cytosolic (ICF) concentration of sodium ion was found to be increased (Mattys *et al*., 2008) while its concentration was said to decrease in the ECF (Rajapurkar, 1994; Kakkilaya, 2003; Mutuku *et al*., 2009).

The pathophysiology of hyponatraemia in malaria remains unclear but several studies have suggested that increased secretion of vasopressin, either appropriately or inappropriately, plays an important role (Miller *et al*., 1967; Sowunmi *et al*., 2000; Hanson *et al*., 2009). Other suggested mechanisms are absolute sodium deficit due to cerebral salt wasting, excessive sweating or loss in the gastrointestinal or urinary tract (Sowunmi, 1996), and the secretion of vasopressin which can be either appropriate, in case of volume depletion (Hanson *et al*., 2009), or inappropriate as in the syndrome of inappropriate antidiuretic hormone secretion (Sowunmi *et al*., 2000) or reset osmostat (Miller *et al*., 1967). There is, however, no consensus as to their relative contributions.

In this study it was observed that there was a significant (P<0.05) increase in plasma potassium in the malaria infected patients when compared to the control subjects. The elevated plasma potassium level observed in the malaria patients positively correlated with the degree of parasitaemia and is experienced irrespective of age or sex. This result is similar to that earlier observed by Nand, *et al*., (2001) on patients with *P. falciparum* infection, and also partly corroborates the findings of Ogbadoyi and Gabi (2007) where significantly (P<0.05) elevated plasma potassium levels were found in male children. The results however differs from that obtained by Wiwanitkit (2007) who documented no significant change (P>0.05) and correlation in serum potassium levels in patients with falciparum malaria and that obtained by Ikekpeazu *et al*., (2010), where a significant lowering of serum potassium was discovered in *P. falciparum* infected patients.

Compartment analysis of infected cells revealed that the cytosol of the host cell is poor in potassium and rich in sodium and that this relationship is reversed in the parasite and the serum, indicating an ability for independent regulation of ionic composition by the parasite (Wiwanitkit, 2007; Matthys *et al*., 2008). White and Kilbey (1996) who reported that host cells lose up to 75-80% of their normal potassium content during the course of a malaria attack also gives credence to why an elevation of potassium in the serum or plasma is sometimes observed in malaria patients. Alappa *et al*. (1996) reported that potassium being solely excreted by the kidneys could become elevated in plasma if any dysfunction in the kidney is experienced as this would result in its reduced excretion, this may account for the elevated K^+ levels in malaria subjects with kidney disease. The elevated plasma potassium levels found in this present study can be therefore be due to rapid haemolysis of malaria-infected red blood cells and the inability of the malaria-compromised kidneys to properly regulate and keep the serum potassium levels within healthy limits.

Our study also observed that there was a significant (P<0.05) metabolic acidosis (decreased plasma bicarbonate-HCO_3^-) in the malaria infected patients. The metabolic acidosis observed in the malaria patients was found to be negatively correlated with the degree of parasitaemia. These findings are in agreement with the findings of the earlier study carried out by Nand *et al*. (2001) where renal dysfunction was found to be more in patients with *falciparum* malaria with heavy parasitaemia. They also found that these patients had a bicarbonate level <20mmol/L indicative of low bicarbonate with the patients expressing features of metabolic acidosis. The findings of this present study partly agrees with the earlier studies of Adeosun *et al*. (2007) on parasitaemic children from South Western Nigeria, where plasma bicarbonate levels in the parasitaemic children were significantly lower (P<0.05) than that in the non-parasitaemic controls but this elevation was not found to increase with increasing parasitaemia. Also, Ogbadoyi and Gabi (2007) have reported in Minna, Nigeria that metabolic acidosis was found only in children.

The World Health Organisation (WHO) already recognizes a plasma bicarbonate concentration of less than 22mmol/L as metabolic acidosis, and recognizes it as one of the severe manifestation and complications of *P. falciparum* malaria (WHO, 2000). Metabolic acidosis has long been associated with *Plasmodium falciparum* malaria with renal involvement ranging from mild proteinuria to severe azotaemia. The metabolic acidosis seen in this present study may result from possible retention of acidic end products of metabolism, hyperventilation, and lactic acidosis from fever and rigors and associated increase catabolic activity following *Plasmodium falciparum* infection complicated by depressed renal function (Boonpucknavig and Sitprija, 1979; Mishra *et al*., 2007; Mishra and Das, 2008). Trampuz *et al*. (2003) in his clinical review has indicated that metabolic acidosis was one of the common systemic complications of *Plasmodium falciparum* malaria.

This study also observed a significant (P<0.05) elevation in the levels of plasma urea and BUN in the *Plasmodium* infected patients. The elevated levels of plasma urea and BUN observed in the malaria patients are positively correlated to degree of parasitaemia and expressed irrespective of the age or sex of the patients. These findings are also in agreement with the earlier study of Nand *et al*. (2001) where raised blood urea was found in patients with severe falciparum malaria with an excellent correlation between hyperparasitaemia and increase in blood urea. The findings of this present study also agrees with the earlier study carried out by Onyeneke *et al*. (2003) where serum urea levels were found to be higher during severe parasitaemia with the male subjects showing significantly raised levels of urea (P<0.01) when compared with the females. The findings of this present study are however partly in agreement with the results of Ekeanyanwu and Akpoilih (2010) on children in Owerri, Eastern Nigeria, where it

was observed that the levels of serum urea, was significantly higher in infected children when compared with the respective control values. The relationship between malaria parasitaemia and serum urea was however negatively correlated. It also partly agrees with results of Ogbadoyi and Gabi (2007) in Minna, Nigeria and Idonije *et al*. (2011) where significant (P<0.05) elevation in blood urea was found in female malaria patients. Values generally obtained for females were found to be lower than that of male counterparts. This study also partly corroborates the findings of Adeosun *et al*. (2007) in children from South Western Nigeria, where plasma urea levels in the parasitaemic children were significantly elevated (P<0.001) than that in the non-parasitaemic controls but this elevation was not found to increase with parasitaemia.

The findings of elevated plasma urea and blood urea nitrogen (azotaemia) in this study can be attributed to various factors like dehydration, increased catabolism and impaired renal function. There is increased excretion of nitrogen and at first decreased elimination of phosphates in *falciparum* malaria patients. Infected erythrocytes take up amino acids at a greater rate than uninfected cells and thus there is a decrease in the accumulation of amino acids (Wernsdorfer and McGregor, 1988). Urea being the end product of protein metabolism and the principal form in which nitrogen is excreted by the body therefore increases due to this increase in amino acid/protein metabolism (Wernsdorfer and McGregor, 1988). During malarial attack, a decrease in plasma protein level has been observed and albumin concentration falls (Thurnham *et al*., 1983). Protein deficiency is very high, and this is due to the fact that there is excessive body protein catabolism in fever, one of the symptoms of malaria. Episodes of acute malaria infection are thought therefore to cause an increase in the levels of serum urea (Philips, 1984).

Our results also observed a significant (P<0.05) elevation in plasma creatinine in malaria infected patients. The elevated level of plasma creatinine observed in the malaria patients, positively correlated with the degree of parasitaemia and is experienced irrespective of age or sex. These findings are in agreement with the earlier findings in *Plasmodium falciparum* malaria infected children in Owerri, Eastern Nigeria obtained by Ekeanyanwu and Akpoilih (2010), that of Nand *et al*. (2001) in Haryana, India and that of Idonije *et al*. (2011) in Ekpoma, Nigeria, where raised plasma creatinine levels were found in patients with severe falciparum malaria with an excellent positive correlation between hyperparasitaemia and increase in levels of plasma creatinine. Our results also supports the study earlier carried out by Onyeneke *et al*. (2003) where serum creatinine levels were found to increase significantly in moderate and severe parasitaemia when compared to the control, with this increase being more in the males when compared to the females. The results also is partly in agreement with earlier study of Adeosun *et al*. (2007) on children from South Western Nigeria, where it was found that plasma creatinine levels in the parasitaemic children were significantly elevated (P<0.001) than that in the non-parasitaemic controls but this elevation was not found to increase with increasing parasitaemia.

The elevated plasma creatinine found in this study could be attributed to various factors, like increased catabolism and impaired renal function (Nand *et al*., 2001). Episodes of acute malaria infection are thought to cause an increase in the levels of serum creatinine (Phillips, 1984). In Thailand, Philips (1984) showed that about a third of adult patients with cerebral malaria had elevated creatinine.

The findings of this study are striking. The results indicate a possible impairment in renal function in these malaria patients. The azotaemia, metabolic acidosis and significantly elevated plasma creatinine levels observed in this study is enough to conclude that the kidneys of these malaria patients may be impaired. This is further confirmed by the hyponatraemia, significantly elevated plasma potassium and blood urea nitrogen levels, as they exist with the former as markers of impaired renal function.

Considering the fact that these patients were not known to suffer from any other ailment apart from malaria (hospital records), it can be said that this study reveals that infection with *Plasmodium falciparum* parasite leads to a kind of renal impairment in these patients within Benin metropolis, South-South Nigeria, which if not properly managed could progress to renal failure. Physicians may therefore be advised to perform routine kidney function tests for their malaria patients especially those whose conditions appear to be severe, resistant, or prolonged in terms of recovery time as they may be experiencing a complication of malaria infection in their kidneys! The results of such tests can lead to proactive interventions that will reduce recovery time and prevent fatal consequences. More study should be carried out to broaden the knowledge and elucidate the exact

pathophysiology of how malaria causes renal disorders in our local environment.

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