Evaluation of Renal Blood Flow Using Doppler Sonography in Children with Acute *Falciparum* Malaria in South-Western Nigeria

Ademola J. Adekanmi[1], Omolola M. Atalabi[1*], Adebola E. Orimadegun[2] and Nathanael B. Afolabi[3]

[1]*Department of Radiology, College of Medicine, University College Hospital, University of Ibadan, Ibadan, Oyo State, Nigeria.*
[2]*Institute of Child Health, College of Medicine, University of Ibadan, Ibadan, Nigeria.*
[3]*Department of Epidemiology and Medical Statistics, College of Medicine, University of Ibadan, Ibadan, Nigeria.*

Authors' contributions

This study was carried out in collaboration between all authors. Author OMA conceived the study, authors OMA and AEO designed the study. Author AJA wrote the Doppler protocol. Authors AJA and OMA carried out the Doppler ultrasound and carried out the data collection. Author AEO supervised the care of the children with malaria and with NA did the data analysis. Author AJA wrote the manuscript and managed the literature searches. Author OMA proof read the manuscript. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: Renal blood flow evaluation during malaria illness is rarely done despite the high incidence of kidney injury from malaria and availability of Doppler ultrasound scanners in malaria endemic areas.
Aims: This study is to evaluate the renal blood flow changes using Doppler ultrasonography among uncomplicated and complicated malaria subsets of pediatric patient with laboratory

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Corresponding author: Email: omatalabi@comui.edu.ng, omotalabi@yahoo.co.uk;

evidence of malaria parasitemia and without background clinical and laboratory evidence of renal impairment. And to compare these with parameters of age matched healthy pediatric control.

Study Design: This was a prospective case control study of renal Doppler indices in children with acute malaria.

Place of Study: The study was conducted among pediatric patients presenting at the children outpatient clinics, emergency and pediatric wards of the University College Hospital (UCH), Ibadan Nigeria.

Methodology: Doppler indices of 602 kidneys were evaluated among 85 uncomplicated (UM), 85 complicated malaria (CM) children that presented within 24 hours and follow up scans on days 3 and 5 of their illness. These were compared with that of 131 healthy children (control).

Results: The main renal artery diameter of the CM group was 0.41±0.07 mm, UM=0.48±0.09 mm and 0.53±0.11 mm (p=<0.001) in the control group. The main renal vein diameter were 0.59±0.11 mm and 0.48±0.10 mm and 0.63±0.15 mm (P=<0.000) among the CM, UM and the control group respectively. The PSV and EDV were slightly lower in the malaria groups than in the control group. PSV=49.01±18.21 cm/s in the UM and CM=50.71±19.68 cm/s. The control group PSV was 56.95±15.47 cm/s. AT was however significantly lower in the two malaria subgroups than in the control. (UM=47.70±18.28 cm/s, CM=52.33±21.06 cm/s and control=75.20±27.66 cm/s respectively (p=<0.000). The Intrarenal S/D in UM was 2.73±0.49 and the CM group S/D was 3.05±0.65 and control=2.62±0.47 (P=0.04). Slightly lower but statistically insignificant mean values were seen in the RI and PI.

Conclusion: The main renal arterial and vein diameters and the intra renal vessel AT are significantly reduced during acute *falciparum* malaria illness. The intra-renal PSV and EDV are likely to be lower in acute *falciparum* malaria than in the normal healthy children. The intra-renal S/D are significantly higher in the UM and CM. Also, the PI and RI are likely to be higher in the malaria groups. The AT and S/D both showed inverse and direct relationship respectively as malaria severity worsens. We propose that renal Doppler ultrasound can be used to monitor renal status and should be included in the management of children with acute malaria infection more so in malaria endemic area.

1. INTRODUCTION

Malaria is a major public health problem with serious socio-economic and developmental implications in tropical countries [1]. About 20% of children admitted in a typical tropical children emergency ward present with severe forms of malaria and/or its complications [2]. The sub-Sahara Africa is documented to account for up to 90% of the reported cases and 85% of the deaths from malaria [3] with *P. falciparum* infection as the cause of almost all cases of deaths due to severe malaria. The 2011 World Malaria Report reported an estimated 655,000 deaths with a range of 490,000 to 836,000 in 2010, mostly among African children [4]. It was reported that a child dies every minute from malaria in Africa. Documented pathophysiologic mechanisms in severe *falciparum* malaria include parasitized red blood cell destruction, acute phase reactions and cytokine up-regulation resulting in likely inflammation [5]. The intravascular red blood cells destruction leads to the release of hemoglobin and other toxic metabolites [5-6] and this process affect virtually all the vital organs of the body including the kidneys and their vessels.

Malaria effect on the kidneys may lead to tubulo-interstitial damage and glomerulonephritis as well as nephrotic syndrome [7-9]. Malaria in addition may result in chronic and progressive nephropathy and acute renal failure which has been associated with *P. falciparum* [10]. It is known that endotoxins including cytokines released during malaria illness increases ischemic renal injury [11] resulting in swelling of the kidneys, blockage and damage to the renal tubules. Also, in severe malaria; there is hypovolaemia from increased vascular permeability with increased blood viscosity due to rigidity of parasitized red cells and increase in acute phase protein. All these result in renal impairment with subsequent reduction in renal blood flow [12] which may cause renal infarction with a possibility of long term kidney damage. Therefore early detection of these effects is important in order to avoid acute renal injury progressing to chronic renal failure.

Previous measurements of renal blood flow (RBF) in humans were done by indirect method of clearance techniques with para-aminohippuric acid (PAH) or a radioisotope tracer [13]. PAH estimation involves correction for haematocrit and PAH extraction thereby affecting the accuracy of RBF measurement and also rendering this method unsuitable in chronic renal failure [14]. In addition the complexity of the technique of numerous timed blood and urine sample collection and non availability for routine clinical use [13], has greatly limited its use in patient care. Nuclear radioisotope clearance methods are also equally technically complex. These challenges have stimulated research for a method that would allow for direct measurement of RBF. In more recent times, other imaging modalities such as, computed tomography, magnetic resonance imaging with arterial spin tagging [13-16], electron beam computed tomography [17], positron emission tomography [14-19] have been shown to noninvasively measure RBF, however these methods are expensive and not widely available especially in the developing world and poses the risk of contrast agent related toxicity [13]. Lately, Doppler ultrasonography has been widely used to study renal blood flow in various disease conditions in the adult [20-29]. In the paediatric population, assessment of renal blood perfusion were also previously indirectly carried out through renal function studies by estimation of the serum creatinine and urea as well as the relatively expensive and time-consuming clearance tests and nuclear medicine [29].

Renal blood flow in malaria had been reported using 133Xe clearance method [30] and radiological studies such as angiography and contrast urography [31] with these studies indicating reduction in cortical perfusion during the acute stage of malaria [30-33]. The introduction of color Doppler ultrasound to pediatric imaging, offers a bedside method of evaluating the renal blood flow [34-36] even in small and critically ill paediatric patients [33] and has the advantage of being cheap, reproducible and ionizing radiation free, It has also widely been used in the study of flow indices in several kidney pathologies [20-29] and provides physiologic information on the arterial blood flow and resistance in the renal arteries [37].

Documented parameters obtained by renal Doppler blood flow in various renal pathologies include; peak systolic volume (PSV), end diastolic volume (EDV), systolic to diastolic (S/D) ratio, resistive index (RI), Pulsatility index (PI) (also referred to as resistivity index or resistance index and Pourcelot index respectively), Acceleration time (AT) and time average mean velocity (TAM). These indices reflect the blood flow in the renal arteries in relation to the cardiac cycle. Colour Doppler can measure precisely the velocity and direction of blood flow through the renal arteries, even in the small caliber renal arterial branches. The RI and PI are commonly used as these parameters reflect vascular impedance [38]. RI though affected by several factors including pathologies and the cardiac cycle phase [38], has been extensively used in the determination of blood flow changes in various renal pathologies [20-29]. PI is reported to give more information about renal flow since it takes into account the mean velocity of the artery [39] while AT has been reported to be valuable in renal artery stenosis, acute renal failure and renal transplant rejection [27,40-42]. Since severe malaria could lead to acute kidney injury, the AT may also be an important Doppler index.

Among children, Doppler ultrasonography has been reported in literature to be useful in the evaluation of renal allograft after rejection, dysplastic kidney, renal artery stenosis and acute kidney injury [43-49] as well as in differentiation of obstructive urinary disease [49,50].

There is however dearth of literature on the renal blood flow evaluation using Doppler sonography in malaria including pediatric population. This study is therefore aimed at unraveling the renal blood flow changes using Doppler ultrasonography among uncomplicated and severe malaria (severe malaria anemia and cerebral malaria) subsets of pediatric patient with laboratory evidence of malaria parasitemia and without background clinical and laboratory evidence of renal impairment. These results were compared with parameters of age matched healthy pediatric control.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This was a prospective case control study. The study was conducted among pediatric patients presenting at the children outpatient clinics, emergency and peadiatric wards of the University College Hospital (UCH), Ibadan Nigeria. Children who presented with fever and were microscopically confirmed to have *Plasmodium falciparum* malaria infection

constituted cases. The controls were healthy children who did not have symptoms and have negative microscopic blood film for *Plasmodium falciparum*. The control group was enrolled from schools in Ibadan. The pediatrics Department in UCH admits about 2500 children annually and about 11% of them are cases of severe malaria. The UCH is a foremost tertiary referral hospital located in Ibadan, South-West of Nigeria.

2.1.1 Study population and sampling

We enrolled consecutive children who present with symptoms, signs and laboratory evidence of malaria and classified into uncomplicated and complicated or severe (consisting of severe malaria anemia and cerebral malaria). Complicated malaria was defined as any case of microscopically confirmed parasitaemia and presence of any life-threatening feature as described by World Health Organization. While UM are without life threatening conditions [33].

Cerebral malaria cases were children in unarousable coma for at least one hour in the presence of asexual *P. falciparum* parasitemia with normal cerebrospinal fluid and a Blantyre coma scoreless or equal to 2 was used to define coma status [51]. While severe malarial anemia cases were conscious children with packed cell volume (PCV) less than 16% in the presence of *P. falciparum* parasitaemia [51]. According to the 2006 National Census figure, Ibadan has an estimated population of 2,550,593 [52] with children less than 15 years constitute about 31% of the population [53]. Those whose parents or caregivers declined consent, infants and those above 15 years of age and any child with pre-existing renal disease were excluded but all the children received standard care according to the National guidelines on treatment of malaria [54].

2.2 Sample Size, Data Collection and Laboratory Procedures

For this study, we assumed that the prevalence of renal abnormalities detectable using ultrasound could range from 3% to 5% and that the Odd Ratio for its occurrence will be about 4.0 at 95% Confidence Interval (CI) and statistical power (1-β) of 80%. We estimated 224 children (112 apparently healthy and 112 UM) as controls and 112 cases will be required for the study giving a total of 336 subjects. These estimates were obtained using the Win Episcope 2.0 software. A total of 301 children comprising of 170 children (UM and CM) with confirmed

P. falciparum malaria cases and 131 healthy children (control) were enrolled.

Participant's parents or care givers were informed about the study by trained research nurses and assistants, highlighting their confidentiality and voluntariness after which their consents were obtained. Pre-tested structured record forms were administered to parents or care givers about their children/ ward by trained research nurses and assistants at the time of enrollment. Each child was examined by the pediatrician and record of socio-demographic data, weight and height were recorded. Thick and thin films were made on the same slide for each patient. The thin film was fixed with methanol immediately and the slides allowed to dry, then flooded with Giemsa stain and examined according to protocol for malaria microscopy [55]. The malaria parasites counts were done against 200 white blood cells (WBC) and parasite density was calculated for each patient based on an assumed total WBC of 8000/μL of blood [55].

2.3 Treatments of Study Subjects

Children with severe malaria were treated with intravenous artesunate, 2.4 mg/kg bolus, repeated 1.2 mg/kg after 12 hours and then 1.2 mg/kg daily till the patient can tolerate oral medication and then given oral Artesunate (4 mg/kg) plus Amodiaquine (10 mg/kg) daily for 3 days. Those who had uncomplicated malaria were treated with oral Artesunate (4 mg/kg) plus Amodiaquine (10 mg/kg) daily for 3 days [54]. Those who had severe anaemia were transfused as appropriate, at the rate of 15 ml/kg or 20 ml/kg of packed-cells and whole blood, respectively [54]. None of the patients who participated in the study required renal replacement therapy but they were managed with appropriate intravenous fluid at the maintenance (1000 ml for every 10 kg body weight) plus 400 mL/m^2/24 hr for insensible loss.

2.4 Ultrasonographic Procedures

Both kidneys of the children recruited into the study were first scanned in B-mode by a portable Micromax Sonosite Inc. Bothhell, WA, USA ultrasound scanner with 5–8 MHZ curved array transducer in the supine and decubitus positions to evaluate the position of the kidneys. Ultrasound scanning was done at the patient's bedside, while appropriate treatment based on the malaria group continued. Doppler study was carried out in prone and oblique positions in

transverse and longitudinal planes of the kidneys. The renal vessels were visualized with colour flow (Fig. 1) and the branching of the intra-arterial vessels of the kidney was seen to the level of the arcuate arteries.

The diameters of the main renal vessels were recorded at the hilum. Doppler sonographic evaluation of interlobar arteries was carried out at the upper, middle and lower pole of each kidney. Three consecutive cardiac cycles with identical spectral analysis were used for measurements to eliminate the effect of movements of the kidney with respiration on the angle of insonation and velocities. The children were scanned without sedation. To achieve reproducible measurements, older children were asked to hold breath quietly while younger ones had to be calmed by their parents to prevent restlessness and crying that would have made the scanning technically difficult. Two certified consultant radiologists performed the scan within 24 hours of presentation of the malaria group at the hospital. These radiologists were blinded to the laboratory test results. The degree of agreement between findings reported by the radiologists was evaluated with ten patients scanned (k=0.9) in the pilot study. In all patients the renal artery PSV, EDV, S/D, RI, PI and AT were calculated from sonographic waveforms obtained from arcuate branches of the renal arteries of both kidneys. The Doppler indices from the upper pole, the mid and the lower poles of each kidney were recorded. The mean of these parameters were calculated for the right and left kidneys, the mean value of the two kidneys were also calculated in each partic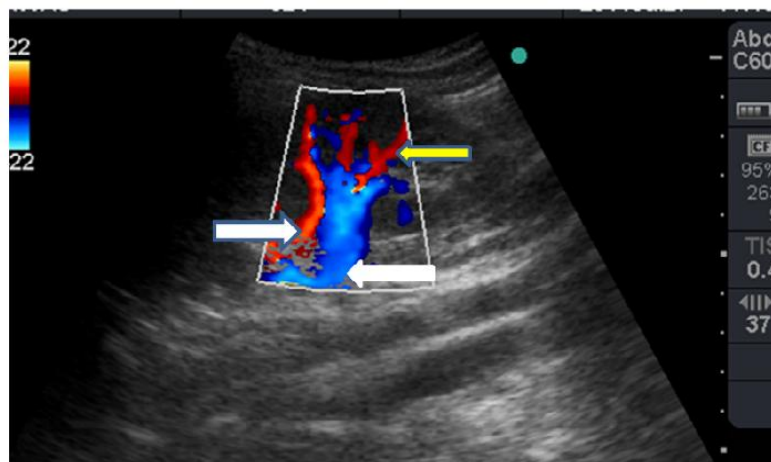ipant [37]. Each ultrasound examination took 20–40 minutes to complete depending on the level of cooperation of the child. The data obtained from uncomplicated malaria and complicated malaria patients (UM and CM) groups were compared with healthy controls.

2.5 Variables, Data Handling and Analysis Plan

All data from subjects with acute malaria on Day 1 scan. And data of those that had complete renal Doppler examination on days 3 and 5 were analyzed. Data was entered in spreadsheet and analyzed using SPSS 20.0 statistical software (SPSS Inc. USA). The main outcome variables measured were main renal artery and vein diameter, the intrarenal PSV, EDV, S/D, RI, PI and AT. Pair wise comparisons of these parameters were done between the control and malaria groups. Level of significant was taken as P value <0.05.

2.6 Ethical Considerations

Participation in the study was completely voluntary and based on written informed consent from parents/ care givers and assent of the children. Participants were made to understand that they are free to withdraw their consent at any time and that they will receive standard level of care. Privacy of participants was censured by using a serial number on the information collected, rather than a name or school register numbers. The study protocol was reviewed and approval for the study was obtained from the University of Ibadan/University College Hospital Ethical Review Committee.

Fig. 1. Colour Doppler sonography of the main renal and segmental vessels
White arrows = main renal arter(red colour)y and vein(blue colour) and the yellow arrow= segmental artery

3. RESULTS

3.1 Characteristics of Study Participants

One hundred and seventy children with confirmed *P. falciparum* malaria (85 uncomplicated, 85 complicated malaria cases) and one hundred and thirty-one (131) healthy children with negative blood film for malaria parasite participated in the study. Table 1 shows the distribution of participants by gender, age, anthropometric and some laboratory parameters. The male to female proportions vary significantly among the different categories of participants with CM group having the highest proportion of 59 males (69.4%) compared with other groups. Whereas there were no significant differences in the mean ages of the UM and CM with a mean age of 49.72 months and 51.07 months respectively, the mean age of the control group was higher than the malaria groups with a mean age of 73.40 months (p=<0.001). For logistic and social reasons we could not recruit age matched children. The mean weight and height also showed similar pattern to the aforementioned age distribution. The mean weight of the children in the control group was 19.56 kg, UM was 14.62 kg and CM 15.31 kg (p=<0.001). Also, the mean height in the malaria group was 94.95 cm and 102.09 in the UM and CM respectively. Children in the CM group had the lowest mean haemoglobin concentration (3.5±0.8 g/l) with significantly varying mean values across the three groups (p<0.001). Forty-two children who had severe anaemia (haemoglobin <5 g/dl) in the CM were transfused with packed red blood cells at 12 to 15 ml per body weight (kg). The malaria parasite counts was also significantly higher in the CM than in UM with a mean count of 133300±99510 counts/µl (<0.001).

The study participants urea levels ranged between 6.7 mg/dl ±1.4, 7.01 mg/dl ±2, 24 and 10.20±4.48 mg/dl among the control, UM and CM respectively (P=0.000). The highest level was recorded in the CM group. All values were however within normal range. The serum creatinine levels of the CM group (0.72 mg/dl ± 0.63) was significantly higher than in the UM and normal groups (0.59 mg/dl ± 0.23 and 0.49 md/dl ± 0.15 respectively) with a P value of 0.001. However the serum creatinine levels of study participants were still lower than the abnormal limit of more than 2 mg/dl, suggesting normal renal function.

A total of four deaths were recorded among the CM group.

3.2 The Main Renal Vessel Diameters

The renal vessels of six hundred and two (602) kidneys from 170 children (UM and CM) with confirmed *P. falciparum* malaria cases and 131 healthy children (control) with negative blood film for malaria parasite that participated in the study had B mode scanning and Doppler ultrasound interrogation. The main renal arterial and vein diameters in the control (healthy children) and the two categories of malaria patients were compared in Table 2. The mean of the main renal artery diameters were significantly different among control and the two subgroups of malaria patients. The main renal artery mean diameter in the CM group was 0.41±0.07 mm, 0.48±0.09 mm in the UM subgroup. The control group mean diameter was 0.53±0.11 mm (*P*<0.000) on day 1. On days 3 and 5 of the malaria illness similar trend of statistically significant lower mean arterial diameters were recorded in the malaria groups than in the control group. Also the CM recorded the lowest mean arterial diameters on these days among the malaria groups, as shown in Table 2. The mean diameters of the main renal veins showed smaller mean diameters comparing the CM, UM and the control groups. The mean diameter of the main renal veins was 0.63±0.15 mm in the control group and 0.59±0.11 mm and 0.48±0.10 mm (*P*<0.000) in the UM and CM respectively.

Table 1. Clinical characteristics of study subjects

	Control (n = 131)	UM (n = 85)	CM (n = 85)	P
Sex: Male (%)	56 (42.7)	48 (56.5)	59 (69.4)	<0.001
Mean Age in months	73.40±25.50	49.72±26.17	51.07±29.02	<0.001
Mean weight (kg)	19.563±5.13	14.620±4.09	15.212±5.46	<0.001
Mean height (cm)	111.46±13.77	94.95±13.96	102.09±18.91	<0.001
Mean haem (g/L)	13.2±0.8	10.7±0.9	8.0±1.6	<0.001
Mean parasite counts/µl	nil	19306±10340	242620±99510	<0.001

*Adjusted for age, sex, weight, height and hemoglobin (for logistic and social reasons we could not recruit age matched children)

3.3 Intrarenal Artery Doppler Parameters in Children with Malaria on Day 1 of Presentation

The mean intrarenal artery Doppler parameters were compared on day 1 of presentation of the malaria illness among the Malaria groups and the control group. The PSV were not significantly different among the malaria groups but were lower than in the control and measured 49.01±18.21 cm/s in the UM and 50.71±19.68 cm/s in the CM group compared with 56.95±15.47 cm/s (*P*=0.10) in the control group. The EDV values differ among the malaria group and the control. Among the malaria groups; CM end diastolic volume was 17.01±7.35 cm/s and 18.22±6.51 cm/s in the UM, while the mean EDV of the control group was 22.31±6.53 cm/s (*P*=0.19). However the S/D ratio of the intra-renal arteries in the CM was higher than that of UM group (CM= 3.05±0.65 and UM=2.74±0.49) and both were higher than that of the control group 2.62±0.47 (*P*=0.04). The intrarenal arterial PI and RI were slightly higher in the CM group [PI=1.11±0.21 and RI=0.65±0.08] than in the UM group [PI=1.0 0±0.19 and RI=0.611±0.07] and both groups showed slightly higher values than in the control but not statistically so as seen in Table 3. The AT values were statistically significant among the CM, UM and the control, with the lowest value recorded in the CM and the largest AT value recorded in the control group (CM=47.70±18.28 cm/s, UM=52.33±21.06 cm/s and control group=75.20±27.66 cm/s with a *P*<0.000).

3.4 Intrarenal Artery Follow-up Doppler Parameters

The mean of the intrarenal artery Doppler parameters on days 1, 3 and 5 in the UM and CM malaria groups were compared as shown in Fig. 2 PSV in UM was 49.02 cm/s, 52.28 cm/s and 55.16 cm/s and in CM 50.89 cm/s, 49.88 cm/s and CM=51.66 cm/s on days 1, 3 and 5. The EDV showed similar trend to the PSV on these days. The Intrarenal S/D in UM was 2.73, 2.9 and 2.99. The CM group S/D was 3.05±65, 2.9±0.59 and 2.94±0.59. The PI among the UM was 1.003, 1.042 and 1.03. However in the CM, the PI was 1.11, 1.001 and 1.08 also on days 1, 3 and 5. The mean Intrarenal RI values were similar to that of the PI. The mean Intrarenal AT

in UM was 52.33, 52.47 and 57.29 while in the. CM it was 47.41, 51.12 and 54.41 on day 1, 3 and 5 of the acute malaria illness.

4. DISCUSSION

Several studies have reported the use of various methods for the evaluation of renal blood flow. These includes para-aminohippuric acid clearance, Magnetic Resonance Imaging with arterial tagging [12,13], Electron beam Computed Tomography [14] and Positron Emission Tomography [15-17] in various diseased conditions. Studies of renal cortical blood flow in malaria illness had also been done using 133Xe clearance method [29] and radiological studies such as angiography and contrast urography [30]. Reduction in cortical blood flow reported from these methods [29,30] during malaria illness. Although Atalabi et al. [56] documented an increase in renal sizes and volumes in children with acute *plasmodium falciparum* malaria on abdominal ultrasonography, this study would appear to be the first to evaluate the renal blood flow changes using Doppler ultrasonography in Nigerian children with acute *falciparum* malaria illness.

A total number of 602 kidneys from control and malaria infected children were evaluated on day 1. This number was reduced to 522 on days 3 and 5 as 40 children with malaria did not complete the study.

This was due to healthcare givers/parents lack of willingness to continue with the study once their wards/children had fully recovered from the instituted malaria treatment, a major constraint in this study. Only the data from those that had complete renal Doppler examination on days 3 and 5 were analyzed.

4.1 Main Renal Vessel Diameter in Acute Malaria

This study clearly showed that the renal artery and vein diameters of the kidneys were comparatively smaller during acute *falciparum* malaria illness than in healthy children i.e. reductions were more marked as malaria severity worsened; with greater reduction in size among those who had complicated than uncomplicated malaria.

Table 2. Main renal vessel diameters among the control and malaria groups

	Day 1				Day 3			Day 5		
	Control	UM	CM	P*	UM	CM	P*	UM	CM	P*
Renal artery diameter	0.53±0.11	0.48±0.09	0.41±0.07	0.000	0.48±0.07	0.42±0.08	0.000	0.50±0.06	0.45±0.07	0.002
Renal vein Diameter	0.63±0.15	0.59±0.11	0.48±0.10	0.000	0.60±0.08	0.50±0.11	0.000	0.61±0.08	0.53±0.10	0.000

Adjusted for age, sex, weight, height and hemoglobin

Table 3. Intrarenal artery Doppler parameters in children with malaria on day 1 of presentation

Intra renal artery Doppler parameters	Control and malaria subgroups			
	Control (n = 130)	UM (n = 85)	CM (n = 84)	P*
Renal artery PSV (cm/s)	56.95±15.47	49.01±18.21	50.71±19.68	0.101
Renal artery EDV (cm/s)	22.31±6.53	18.22±6.51	17.01±7.35	0.195
Renal artery S/D	2.62±0.47	2.74±0.49	3.05±0.65	0.044
Renal artery PI	0.94±0.13	1.00±0.19	1.11±0.21	0.105
Renal artery RI	0.60±0.06	0.611±0.07	0.65±0.08	0.196
Renal artery AT (cm/s)	75.20±27.66	52.33±21.06	47.70±18.28	0.000

Adjusted for age, sex, weight, height and hemoglobin

Although these reductions were reversed to almost normal healthy values by day 5. Since this could not be corroborated with previous similar studies, we can only infer that the diameter reduction may be due to vasoconstriction which might have been caused by the release cytokines and other metabolites during the malaria infection. In addition, there was progressive increase in the renal vessel diameters of the UM and CM groups, compared to day 1 values on day 3 and 5 with these diameters approaching that of the healthy children's. We postulate that this may be due to resolution of the malaria illness and the vasoconstriction effect with instituted treatment over these days. Furthermore this study showed that the main renal veins were generally larger than their arterial counterpart both among the malaria groups and the healthy children. This is in agreement with studies reported by Sataypal [57] and Hazirolan et al. [58].

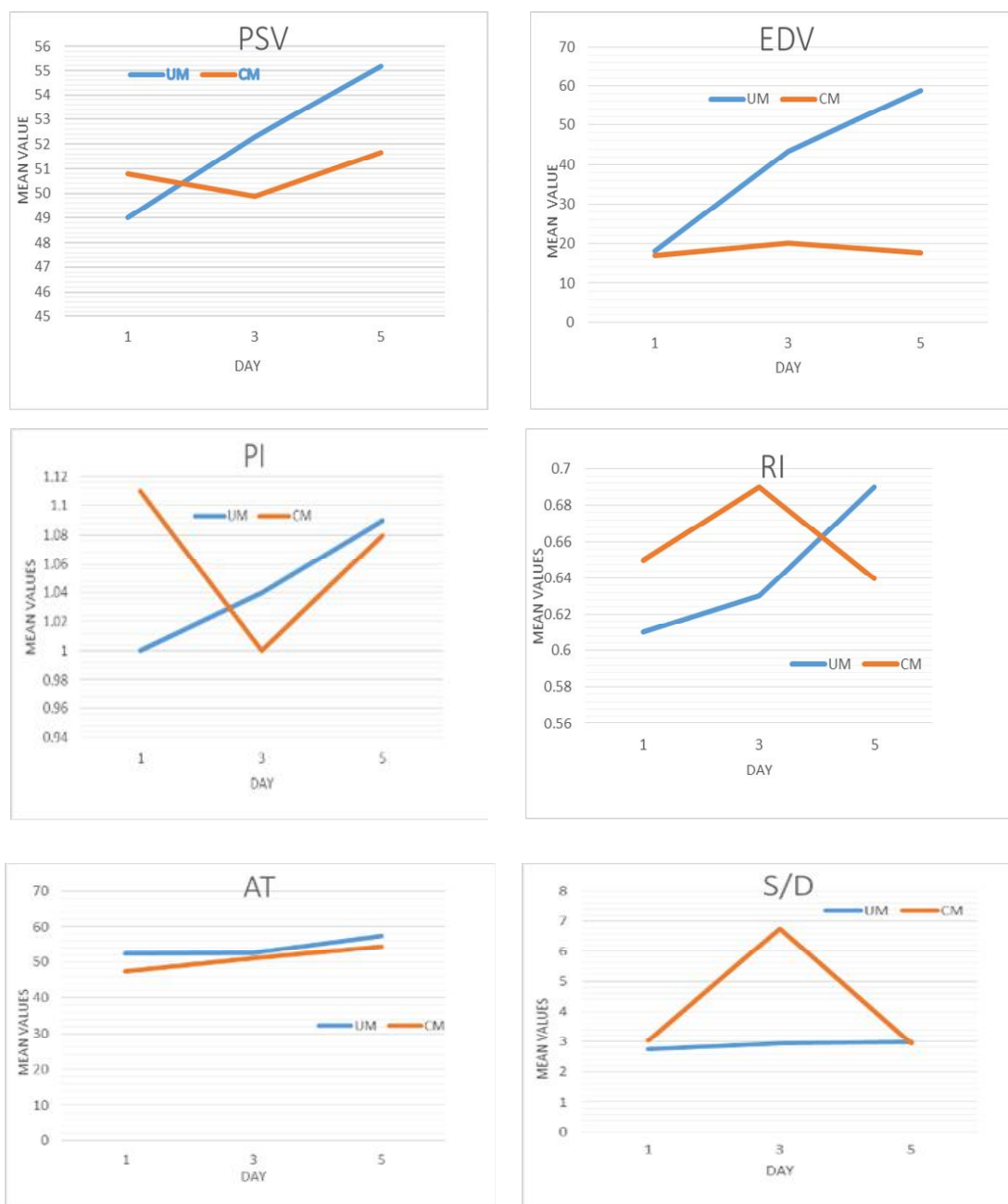## 4.2 Intrarenal Doppler Parameters in Acute Malaria

This study also showed that the intrarenal arterial blood flow velocities were affected by acute *falciparum* malaria but to varying degrees when compared with the healthy children (control). The peak systolic velocity (PSV) and the end diastolic velocity (EDV), indicating the flow of blood in the kidneys during systole and diastole respectively were slightly reduced during an acute *falciparum* malaria illness. The mean PSV was slightly lower in the UM and the CM than the in the control group but no significant difference exist in the PSV values in the malaria group. The mean EDV were also lower in the malaria groups than in the control. Within the malaria groups, the EDV were lower in the CM than in the UM group indicating that reduction in the EDV becomes more marked as the malaria illness worsened from uncomplicated to complicated malaria. Furthermore, there were significant reductions in the acceleration time (AT) in the malaria subgroups compared to the healthy children. The decrease in the AT appears to be proportional to the malaria severity as evidenced by the CM group recording the lowest AT value amongst the two malaria groups. These changes in PSV, EDV and AT again may be due to the destruction of parasitized red cells with release of hemoglobin and toxic metabolites, increased viscosity [5,6] with resultant slowing of the blood flow and or renal swelling associated with the release of endotoxins and malaria pigments during the malaria illness [11] and documented renal blood flow reduction effect of malaria [12]. The reduction in EDV may also be due to increase vessel resistance from the known vasoconstriction effect of malaria. The EDV and the AT were not only lower in the malaria groups in the acute phase of *falciparum* malaria illness than in healthy children but also showed much lower values as the severity of malaria worsens. This progressive decrease in EDV and AT as the malaria severity worsens corroborates the fact that malaria severity affects the flow of blood in the kidneys.

The S/D (ratio of the PSV to EDV), the PI and the RI, all indicators of vascular resistance showed similar trends. The S/D alone showed significantly higher values in the malaria groups than in the healthy group. Also within the malaria subgroups, the S/D was significantly higher in the CM than in the UM group in both kidneys. The S/Ds were significantly higher in acute malaria and also depict a direct proportionality to malaria severity. The PI and RI were also slightly higher in the malaria groups than in the healthy children with higher values seen in the CM among the malaria groups. This study suggests that the S/D (PSV/EDV) is a more sensitive indicator of renal blood flow than either PSV or EDV alone.

4.3 Follow-up Doppler Parameters of the Intrarenal Arteries in Malaria

Follow-up Doppler parameters on day 3 and day 5 showed that there is persistence of the low PSV, EDV and AT with marginal increase in their values on day 5 indicating gradual return to the healthy children values, presumably due to ongoing resolution of the malaria illness from the instituted malaria treatment. On the other hand, the S/D, PI and RI still show higher values than that of the healthy controls even on day 5. Hence, persistently decreasing AT and increasing S/D therefore would be a pointer to progression to worsening/more severe malaria infection We could not deduce from this study on what day did these Doppler parameters showed reversal to that of the healthy children (control group) range due to the very poor turnout for follow up Doppler ultrasound scan after day 5. Further studies would be needed, particularly in the follow up for more days to determine when these Doppler values actually return to the healthy children values.

Fig. 2. Line graph showing Intra-renal artery Doppler parameters on day 1, 3 and 5 among the UM and CM malaria groups

4.4 Serum Creatinine and Doppler Parameters

This study has also shown that renal Doppler blood flow changes may precede changes in the serum creatinine as evidenced by the serum creatinine were normal in all study participants, though higher in the CM group.

5. CONCLUSION

This study has shown that acute malaria may more likely affect renal vessel diameter and the intrarenal blood flow indices in the kidneys. From this study renal Doppler blood flow changes may be an early pointer or predictor of acute kidney injury during acute malaria illness. Renal Doppler

ultrasound should therefore be considered as part of management especially in children with complicated malaria particularly on days 1 and 5 for diagnostic and prognostic evaluation of the kidneys, more so in malaria endemic area.

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COMPETING INTERESTS

The authors declared no conflict of interest.

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