Original Article

Plasma Urokinase Plasminogen Activator and Pro-Adrenomedullin as Biomarkers in Hypertensive Individuals with Malaria Co-Infection at Nauth, Nnewi, Nigeria

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Abstract

Background: Hypertension (HTN) and malaria remain major causes of comorbidity and mortality in low- and middle-income countries (LMICs), including Nigeria. The coexistence of these conditions poses a significant double disease burden. Malaria infection may influence hypertension progression, possibly through inflammatory and endothelial pathways. This study aimed to evaluate plasma levels of urokinase plasminogen activator (uPA), a serine protease involved in fibrinolysis and tissue remodeling, and pro-adrenomedullin (Pro-ADM), a precursor of a vasoactive peptide associated with endothelial function, in hypertensive individuals with and without malaria infection.

Methods: This cross-sectional study was conducted at NAUTH, Nnewi, Nigeria, and included 90 participants aged 22–79 years. Participants were grouped into 30 hypertensive individuals with confirmed *Plasmodium*

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falciparum malaria infection, 30 hypertensive individuals without malaria, and 30 apparently healthy controls (46 females and 44 males). Five milliliters of venous blood was collected from each participant. Malaria diagnosis was performed using Giemsa-stained thick and thin blood smears. Plasma uPA and Pro-ADM levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA). Exclusion criteria included HIV infection, diabetes mellitus, chronic kidney or liver disease, pregnancy, or other acute infections.

Results: Hypertensive individuals with malaria infection had significantly higher mean plasma levels of uPA (7.02±3.57 ng/mL) and Pro-ADM (52.02±27.23 pg/mL) than hypertensive individuals without malaria (2.14±0.52 ng/mL, 20.39±2.34 pg/mL) and healthy controls (2.39±2.48 ng/mL, 21.23±2.51 pg/mL) (p = 0.000 respectively). A significant positive correlation (r = 0.640, p = 0.000) was observed between uPA and Pro-ADM levels in the malaria-infected hypertensive group.

Conclusion: The concurrent elevation of uPA and Pro-ADM in hypertensive individuals with *Plasmodium falciparum* infection may suggest a combined response to endothelial dysfunction and inflammatory stress. These findings point to a potential pathophysiological link between infectious and cardiovascular diseases. However, given the cross-sectional design, causality cannot be established. Further longitudinal studies are warranted to explore these biomarker relationships and their clinical implications in malaria-endemic settings.

Keywords: Hypertension, *Plasmodium falciparum*, Urokinase Plasminogen Activator, Pro-adrenomedullin, Endothelial Dysfunction, Comorbidity, Nigeria.

Introduction

Hypertension, commonly referred to as high blood pressure, is a leading global health challenge, contributing significantly to cardiovascular morbidity and mortality. The World Health Organization (WHO) estimates that over 1.28 billion adults aged 30–79 years globally have hypertension, with two-thirds living in low- and middle-income countries[1]. In Nigeria, the burden of hypertension has increased markedly over recent decades, owing to lifestyle changes, urbanization, and lack of awareness or effective management[2]. The situation becomes more complex when hypertension coexists with infectious diseases endemic to sub-Saharan Africa, such as malaria[3].

Malaria remains a major public health concern in Nigeria, which accounts for approximately 25% of global malaria cases[4]. Plasmodium falciparum, the most prevalent species in Nigeria, is known for causing severe and sometimes fatal forms of malaria. The interplay between malaria and hypertension is of emerging clinical interest, especially given that both conditions can influence vascular function, immune response, and endothelial integrity[3, 5]. Co-infection or co-existence of malaria in hypertensive individuals may exacerbate systemic inflammation, endothelial dysfunction, and coagulation abnormalities. There has been an inter link between hypertension and high risk infectious disease such as malaria. The general view that malaria being endemic in the low-income countries, coupled with observations that non communicable diseases like hypertension are often associated with harsh economic and environmental conditions, have provided a basis for speculations for the possible linkage between malaria and hypertension [3]. Urokinase plasminogen activator (uPA) and pro-adrenomedullin (pro-ADM) are biomarkers and therapeutic targets which have been associated to play specific roles relating to vascular function and blood pressure regulation. However, the exact mechanisms and clinical implications of these biomarkers in hypertension with relation to malaria infection have not been completely understood. In this context, biomarkers that reflect endothelial activation, inflammation, and fibrinolytic balance are essential for understanding disease progression and possible interactions. Urokinase-type plasminogen activator (uPA) is a serine protease that plays a critical role in fibrinolysis, tissue remodeling, and cellular migration[6]. It is involved in the conversion of plasminogen to plasmin and has been implicated in both vascular remodeling in hypertension and immune responses during infections [7]. Elevated uPA levels may signal heightened fibrinolytic activity or inflammatory responses, which are key components of both hypertensive pathophysiology and malaria infection[8]. It's soluble form, suPAR, has potent proinflammatory and chemotactic properties with highly stable serum levels. It has been reported that serum suPAR levels are elevated in acute inflammatory processes, such as sepsis, systemic infection, and malignancy, as well as in chronic inflammatory processes, such as diabetes, glomerulosclerosis, and cardiovascular disease[9].

Pro-adrenomedullin (pro-ADM), a stable precursor of adrenomedullin, is a peptide with potent vasodilatory and immunomodulatory properties with several metabolic effects [10]. It has gained attention as a biomarker in cardiovascular diseases and sepsis and is associated with endothelial dysfunction and severity of disease states[11]. Elevated plasma levels of pro-ADM have been reported in hypertensive individuals and patients with infectious diseases, including malaria [12]. It serves as a marker of systemic inflammation and endothelial stress, both of which are crucial in understanding hypertension and malaria interactions.

Adrenomedullin is a hormone with blood pressure lowering effect including vasodilation, diuresis, natriuresis, increasing capillary permeability, and aldosterone inhibition [13]. The most important functions of AM in the vasculature are vasodilation and the maintenance of vascular integrity. Adrenomedullin is thought to maintain vascular tone through direct action on vascular smooth muscles cells and the formation of nitric oxide. The vasodilative ability of AM is as strong as that of ANP. The administration of AM decreases blood pressure in vessels but increases blood flow[14]. Adrenomedullin is a potent vasodilatory peptide that is overexpressed in many cardiovascular diseases, including pulmonary hypertension (PH). Previous research has provided evidence suggesting that adrenomedullin administration may attenuate PH in animal models, and might even improve hemodynamics in PH patients[15]. Although ADM is secreted from various organs and tissues, it is produced mainly by vascular endothelial cells and serves a number of physiological functions. Of note, plasma ADM levels are elevated in patients with hypertension, congestive heart failure or myocardial infarction, renal disease, diabetes mellitus, the acute phase of stroke, septic shock, arterial stiffness, and the magnitude of the elevation is in proportion to the severity of the disease involving vascular damage[16].

Despite the individual significance of these biomarkers in hypertension and infectious diseases, limited studies have investigated their combined behavior in hypertensive patients with concurrent malaria infection. Understanding the plasma levels of uPA and pro-ADM in such patients could provide novel insights into the inflammatory and vascular burden imposed by this comorbidity. This is particularly important in Nigeria, where malaria is endemic and hypertension prevalence is rising hence, the study design.

Materials and Methods

Study Area

This research was carried out in Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State, Nigeria.

Study design

This cross sectional study was conducted to assess the serum levels of urokinase plasminogen activator (uPA) and pro-adrenomedullin in hypertensive individuals with and without malaria attending the cardiovascular health clinic in Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State, Nigeria. Selection of individuals was by random sampling. Written consent (questionnaire) was obtained from the individuals and the individual's request form was used to get their bio-data. A total of 90 subjects was recruited for the study which includes 30 hypertensive individuals with malaria, 30 hypertensive individuals without malaria and the control group, 30 non-hypertensive without malaria.

Study recruitment

The individuals for this study were recruited at Internal medicine (cardiovascular unit), Nnamdi Azikiwe university teaching hospital (NAUTH) Nnewi, Anambra state Nigeria. Permission was obtained from participants and selection was by random sampling whereby Questionnairres were given to the subjects to fill out and the patient's request form were used to obtain their bio-data.

Inclusion nd Exclusion criteria

The inclusion criteria for this study were both male and female hypertensive individuals with and without malaria, non - hypertensive individuals without malaria who were the control individuals, all within the age range of 22-79 years while, the exclusion criteria were individuals outside the age range of 22-79 years. HIV infected individuals were excluded. Participants with diabetes and/or with other metabolic problems were excluded. Pregnant women and children were also excluded from the study.

Ethical clearance and Informed consent

The ethical approval for this research was obtained from board of ethics committee of Nnamdi Azikiwe University Teaching Hospital, (NAUTH), Nnewi with ref: NAUTH/CS/66/VOL.17/VER.3/61/2024/196 in accordance with the Helsinki declaration by the World Medical Association (WMA) on the ethical principles for medical research involving human subjects.

Sample collection

About Five (5) ml of venous blood was collected for this study. Plasma was extracted after centrifugation at 5000 RPM for 4 minutes. Samples were stored at 4 Degree centigrade (4°c) before analysis.

Methods

Screening for malaria infection

Principle: The individuals were screened for Malaria infection using Giemsa staining technique. The ingredients in Giemsa solution include eosin and methylene blue (azure). The parasite nucleus is stained red by the eosin component and blue by the methylene blue component. Methanol is used to fix the thin film. The thick film's dehaemoglobination and staining happen simultaneously

Measurement of blood pressure

Blood pressure was measured using the mercuric sphygmomanometer. The individual was made sure not to have any trauma in that arm. The individual ensured to be relaxed and seated comfortably with their back supported and foot uncrossed and flat on the floor. The BP curf was ensured to be the correct size for the arm and ensured to be in correct level with the persons heart (midsternal level), while being positioned at 2-3cm above the brachial artery. The radial pulse was located and the BP curf inflated. The BP curf was deflated for about 15-30 seconds. The measurement was retaken at 20-30mmhg to estimate the systolic BP and the curf deflated at the rate of 2 mmhg.

Determination of uPA

Principle: An invitro technique for the quantitative measurement of Human urokinase plasminogen activator in plasma, serums, cell lysates, tissue homogenate was determined using ELISA as was described by Smith et al. [17]. This assay employs an antibody specific for Human suPAR coated on a 96 well plate. Standards or samples are added to the micro ELISA plate wells and combined with specific antibody. Then a biotinylated detection antibody specific for Human suPAR Avidin – Horseradish Peroxidase (HRP) conjugate are added successively to each micro plate well and incubated. Free components are washed away. The substrate solution is added to each well. Only those wells that contain Human suPAR, biotinylated detection antibody and Avidin-HRP conjugate will appear blue in color. The enzyme - subsrate reaction is terminated by the addition of stop solution and the color turns yellow. The optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm. The OD value is proportional to the concentration of Human suPAR.

Determination of pro-adrenomedullin

Principle: The pro-adrenomedullin kit is based on sandwich enzyme-linked immune-sorbent assay technology as was described by [18]. An antibody is pre-coated onto a 96 well plate. Standards, test samples and bio conjugated reagents are added to the wells and incubated. The HRP- conjugated reagent is then added, and the whole plate is incubated, unbound conjugates are removed using wash buffer at each stage. TMB substrate is used to quantify the HRP enzymatic reaction. After TMB subsrate is added, only wells that contain sufficient pro-adrenomedullin will produce a blue colored product, which then changes to yellow after adding the acidic stop solution. The intensity of the yellow color is proportional to the pro-ADM amount bound on the plate. The optical density (OD) is measured spectrophotometrically at 450nm in a micro plate reader, from which the concentration of pro-adrenomedullin can be calculated.

Statistical analysis

Data generated from the study was analyzed using SPSS version 25. Qualitative / categorical variables was analyzed using descriptive statistics and values presented as frequency and percentages, quantitative variables were presented as mean ± standard deviation, comparative analysis was carried out using one way ANOVA, post hoc LSD was used to carry out multiple comparison within the groups, test for relationship was carried out using Pearson correlation and values are considered significant at p< 0.05.

Results

Anthropometric and blood pressure variables in hypertensive individuals with/without malaria and apparently healthy controls

The mean value of age, systolic and diastolic blood pressure were significantly higher in hypertensive individuals with malaria (63.93±9.21, 138.87±28.99, 90.60±15.56) and hypertensive individuals without malaria (58.47±10.72, 135.10±18.75, 89.03±10.54) when compared with apparently healthy controls (33.23±9.66, 112.27±4.21, 68.27±6.14) (p = 0.000 respectively) (table 1).

Table 1: Anthropometric and blood pressure variables in hypertensive individuals with/without malaria and apparently healthy controls

Group	Age (Yrs)	BMI (Kg/m2)	SBP (mmhg)	DBP(mmhg)
Hypertensive with malaria (A) N=30	63.93±9.21	28.08±4.35	138.87±28.99	90.60±15.56
Hypertensive without malaria (B) N=30	58.47±10.72	28.11±5.73	135.10±18.75	89.03±10.54
Control (C) N=30	33.23±9.66	29.16±17.02	112.27±4.21	68.27±6.14
F-value	82.322	0.100	14.919	10.378
P-value	0.000	0.905	0.000	0.002
A vs B	0.105	0.470	1.000	1.000
A vs C	0.000	1.000	0.000	0.000
B vs C	0.000	1.000	0.000	0.001

BMI = Body mass index, SBP = systolic blood pressure,
DBP = Diastolic blood pressure, p0.05 = significant.

Gender comparison of anthropometeric and blood pressure variables in hypertensive individuals with/without malaria and apparently healthy controls

The mean values of age and systolic blood pressure was significantly higher in females hypertensive with malaria (62.00±9.42, 139.50±30.13) when compared with apparently healthy female controls (33.56±11.62, 114.31±3.86), also in males hypertensive with malaria (65.63±8.97, 138.31±28.95) when compared with apparently healthy female controls (33.56±11.62, 114.31±3.86) and apparently healthy male controls (32.86±7.22, 110.79±3.90) (p = 0.000 respectively). Similarly, there was significantly higher mean values of age in female hypertensive without malaria (55.84±10.41) when compared with apparently healthy female controls (33.56±11.62) and apparently healthy male controls (32.86±7.22), also in males hypertensive without malaria (63.00±10.13) when compared with females (33.56±11.62) and apparently healthy male controls (32.86±7.22) (p = 0.000 respectively) (table 2).

Table 2: Gender comparison of Anthropometric and blood pressure variables in hypertensive individuals with/without malaria and apparently healthy controls

Group	Age (Yrs)	BMI(Kg/m^2	SBP(mmhg)	DBP(mmhg)
Female hypertensive with malaria (N=14) (A)	62.00±9.42	28.18±4.14	139.50±30.13	81.86±13.83
Male hypertensive with malaria (N=16) (B)	65.63±8.97	27.98±4.65	138.31±28.95	79.50±17.30
Female hypertensive without malaria (N=19) (C)	55.84±10.41	28.65±6.45	135.32±17.77	80.11±10.44
Male hypertensive without malaria (N=11) (D)	63.00±10.13	27.16±4.32	134.72±21.24	77.18±10.95
Female control (N=16) (E)	33.56±11.62	31.93±23.11	114.31±3.86	69.50±5.78

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Male control (N=14) (F)	32.86±7.22	26.00±3.09	110.79±3.90	66.86±6.44
F value	34.565	.526	5.830	4.293
P value	0.000	.756	0.000	0.002
A vs B	1.000	1.000	1.000	1.000
A vs C	1.000	1.000	1.000	1.000
A vs D	1.000	1.000	1.000	1.000
A vs E	0.000	1.000	0.017	0.066
B vsC	0.062	1.000	1.000	1.000
B vs D	1.000	1.000	1.000	1.000
B vs E	0.000	1.000	0.002	0.151
B vs F	0.000	1.000	0.006	0.054
C vs D	0.391	1.000	1.000	1.000
C vs E	0.000	1.000	1.000	0.123
C vs F	0.000	1.000	0.981	0.123
D vs E	0.000	0.865	0.121	1.000
D vs F	0.000	1.000	0.051	0.066
E vs F	1.000	1.000	1.000	1.000

P0.05 = Significant, SBP =systolic blood pressure, BMI =Body mass index, DBP = Diastolic blood pressure

Levels of plasma uPA and Pro-ADM in hypertensive individuals with and without malaria and controls

The mean levels of plasma urokinase plasminogen activator (UPA) and Pro-adrenomullin were significantly higher in hypertensive individuals with malaria infection (7.02±3.57, 52.02±27.23) when compared with their counterpart without malaria infection (2.14±0.52, 20.39±2.34) and apparently healthy controls (2.39±2.48, 21.23±2.51) (p = 0.000 respectively) (table 3)

Table 3: Levels of plasma uPA and Pro-ADM in hypertensive with/without malaria and control

Groups	Human UPA(ng/ml)	PRO-ADM (ng/l)
Hypertensive individuals with malaria (A) (N=30)	7.02±3.57	52.02±27.23
Hypertensive without malaria (B) (N=30)	2.14±0.52	20.39±2.34
Apparently healthy controls (C) (N=30)	2.39±2.48	21.23±2.51
F-value	35.333	38.813
P-value	0.000	0.000
A vs B	0.000	0.000
A vs C	0.000	0.000
B vs C	1.000	1.000

UPA = Urokinase plasminogen activator, Pro-ADM = pro-adrenomedullin

Gender comparison between plasma levels of uPA and Pro- ADM in hypertensive individuals with and without malaria and controls.

The mean levels of human UPA and PRO-adrenomedullin were significantly higher in females hypertensive individuals with malaria (8.85±3.67, 61.92±26.51) and males hypertensive individuals with malaria (5.48±2.66, 43.36±25.54) when compared with females hypertensive without malaria (2.12±0.50, 20.48±2.80), males hypertensive without malaria (2.17±.58, 20.22±1.30) and apparently healthy female controls (2.79±3.38, 21.23±2.79). Similarly, there was significantly higher levels of human UPA in males hypertensive with malaria (5.48±2.66) when compared with apparently healthy male control (1.92±0.30). (p = 0.000 respectively) (table 4)

Table 4: Gender comparison of plasma levels of uPA and Pro-ADM in hypertensive with/without malaria infection

Group	UPA(ng/ml)	PRO-ADM (ng/l)
Female hypertensive with malaria (N=14) (A)	8.85±3.67	61.92±26.51
Male hypertensive with malaria (N=16) (B)	5.48±2.66	43.36±25.54
Female hypertensive without malaria (N=19) (C)	2.12±0.50	20.48±2.80
Males hypertensive without malaria (N=11) (D)	2.17±.58	20.22±1.30
Female healthy control (N=16)(E)	2.79±3.38	21.23±2.79
Male healthy control (N=14) (F)	1.92±0.30	21.23±2.24
F value	19.794	19.236
P value	0.000	0.000
A vs B	0.002	0.018
A vs C	0.000	0.000
A vs D	0.000	0.000
A vs E	0.000	0.000
B vsC	0.000	0.000
B vs D	0.001	0.001
B vs E	0.003	0.001
B vs F	0.000	0.002
C vs D	0.949	1.000
C vs E	1.000	1.000
C vs F	1.000	1.000
D vs E	1.000	0.865
D vs F	0.000	0.869
E vs F	0.312	1.000

Human UPA = Human Urokinase plasminogen activator, Pro-ADM = pro-Adrenomedullin

Correlation between the levels of uPA and Pro-ADM with malaria severity in hypertensive individuals.

There was a significant strong positive correlation between human uPA and Pro-ADM (r=0.640, p = 0.000) in hypertensive individuals with malaria infection. (see table 5)

Table 5: Correlation between the levels of Human UPA, pro-ADM and malaria severity in hypertensive individuals.

Correlation	R	P-value
Huma n UPA(ng/ml) vs PRO-ADM(ng/l)	0.640**	0.000
Human UPA (ng/ml) vs Malaria severity	-.101	0.595
Malaria severity vs PRO-ADM(ng/l)	0.172	0.364

uPA = Urokinase plasminogen activator, Pro-ADM = pro-adrenomedullin

Discussion

This study demonstrates a significant elevation in blood pressure parameters among hypertensive individuals co-infected with *Plasmodium falciparum*, suggesting that malaria may worsen the cardiovascular burden in such individuals. The interplay between infectious and chronic non-communicable diseases, especially in low-resource, malaria-endemic settings like Nigeria, underscores the need to understand shared pathophysiological mechanisms.

A notable finding was the significantly higher mean age among both male and female hypertensive individuals with malaria compared to healthy controls. This aligns with the understanding that aging is associated with increased susceptibility to both hypertension and malaria-related complications. Age-related changes such as immune dysregulation, arterial stiffness, metabolic dysregulation, and cumulative exposure to environmental risk factors may contribute to this pattern[19]. The result also supports previous findings by Eze et al.[20], who reported an age-related relationship between malaria infection and hypertension. Gender differences in biomarker expression may also reflect hormonal influences particularly the protective vascular effects of estrogen and differences in immune response patterns between men and women[21].

The mean systolic and diastolic blood pressures were significantly higher in hypertensive individuals with malaria compared to those without infection. This implies that malaria may exacerbate hypertensive states, potentially through a combination of systemic inflammation, oxidative stress, and endothelial dysfunction[3, 22] . Pro-inflammatory cytokines such as TNF-α and IL-6, commonly elevated in malaria, can impair endothelial nitric oxide production, increasing vascular tone and resistance[23, 24]. Dehydration due to malaria-induced fever and sweating may further raise blood viscosity and vascular load[25]. Sympathetic nervous system activation[26] and malaria-associated renal impairment[27] may also contribute to fluid retention and elevated blood pressure.

In this study, plasma levels of urokinase plasminogen activator (uPA) were significantly elevated in hypertensive individuals with malaria. uPA is a key enzyme in fibrinolysis and extracellular matrix remodeling and may reflect heightened endothelial activation and a pro-thrombotic state[28]. Its increase suggests not only an attempt to prevent clot formation but also an amplified inflammatory response[29]. Similarly, Pro-adrenomedullin (Pro-ADM), a precursor of the vasodilator adrenomedullin, was significantly elevated in the malaria-hypertension group. Pro-ADM is widely recognized as a biomarker of endothelial dysfunction, vasodilation, and systemic stress. Its elevation in malaria-infected hypertensive individuals likely reflects a compensatory response to vascular inflammation and increased arterial stiffness[30, 31]. Elevated Pro-ADM has been associated with severe infections and poor cardiovascular outcomes, further emphasizing its clinical relevance[16, 32, 33].

Both uPA and Pro-ADM were elevated across sexes in the hypertensive-malaria group, indicating a systemic response not limited by hormonal differences. In females, the increased levels may be partially driven by estrogen-modulated immune responses[34], while in males, the findings likely reflect direct effects of systemic inflammation and vascular injury[35]. The observed strong positive correlation between uPA and Pro-ADM supports a synergistic endothelial and inflammatory response. This is consistent with findings by Eze et al.[20] and suggests that these biomarkers may act in concert as part of the host's response to combined vascular and infectious stress.

These results suggest that malaria co-infection may intensify the vascular injury associated with hypertension, potentially accelerating the onset of complications such as stroke, heart failure, or kidney damage[36]. As such, these biomarkers could serve not only as mechanistic indicators but also as prognostic tools in hypertensive patients with malaria in endemic regions.

Conclusion

This study highlights the potential of *Plasmodium falciparum* malaria to aggravate hypertension through systemic inflammation and endothelial dysfunction, evidenced by elevated levels of uPA and Pro-ADM. The positive correlation between these biomarkers suggests a coordinated pathophysiological response to combined cardiovascular and infectious stress. These findings reinforce the need for integrated clinical management strategies that consider the role of infections like malaria in worsening chronic conditions such as hypertension. Further longitudinal research is recommended to clarify causality and validate the prognostic utility of uPA and Pro-ADM in malaria-hypertension comorbidity.

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