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ASSOCIATION OF ACUTE PHASE INFLAMMATORY PROTEIN WITH DIPPERS AND NON DIPPERS BLOOD PRESSURE IN PATIENTS WITH INCIDENT HYPERTENSION

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ABSTRACT

Inflammatory state could play a role in the alterations of circadian rhythm of blood pressure (BP). This study was aimed to evaluate the association of acute phase proteins with dippers and non-dippers blood pressure profile in patients with new onset hypertension. A case control study involving a total of 50 subjects within the age range of 30 to 60 years were recruited. Twenty five (25) subjects had incident blood pressure, while twenty five (25) were normotensive who served as control. The subjects daytime and nocturnal blood pressure were taken a day to the sample collection. Blood samples collected were used in the assay of acute phase proteins; C-reactive protein, fibrinogen, ferritin and haptoglobin using standard ELIZA laboratory procedures. All data obtained in the study were analyzed using student t-test (spss.21) and Pearson correlation coefficient. The level of significance was set at $p < 0.05$. There was no significant difference (p=0.393) in the mean value of CRP in dipper subjects (1.94±0.60)mg/ml when compared to non-dipper subjects (2.23±0.91)mg/ml. There was no significant difference (p=0.288) in the mean value of fibrinogen in dipper subjects (3.72±1.01)mmol/L when compared to healthy non dipper subjects (4.19±0.94)mmol/L. There was no significant difference (p=0.116) in the mean value of ferritin in dipper subjects (2.63±0.39)mg/L when compared to healthy non dipper subjects (2.95±0.49)mg/L. There was no significant difference (0.419) in the mean value of Haptoglobin in dipper subjects (1.17±0.28)g/L when compared to healthy non dipper subjects (1.28±0.32)g/L. The mean value of C-reactive protein was significantly reduced (p=0.002) in hypertensive dipper subjects (3.11±1.39)mg/ml when compared to hypertensive non dipper subjects (6.14±2.20)mg/ml. The mean value of fibrinogen was significantly reduced (p=0.018) in hypertensive dipper subjects (5.32±1.11)mmol/L when compared to hypertensive non dipper subjects (7.04±1.71)mmol/L. There was no significant difference (p=0.067) in the mean value of ferritin in hypertensive dipper subjects (3.51±0.59)mg/L when compared to hypertensive non dipper subjects (4.13±0.78)mgl/L. There was no significant difference (0.239) in the mean value of Haptoglobin in hypertensive dipper subjects (2.25±1.11)g/L when compared to hypertensive non dipper subjects (2.90±1.21)mgl/L. The mean value of C-reactive protein was significantly increased (p=0.019) in hypertensive dipper subjects (3.11±1.39)mg/ml when compared to non-dipper subjects (1.94±0.60)mg/ml. The mean value of fibrinogen was significantly increased (p=0.003) in hypertensive dipper subjects (5.32±1.11)mmol/L when compared to non-dipper subjects (3.72±1.01)mmol/L. Non dipper variation in high blood pressure is associated with increase in C-reactive protein, fibrinogen, ferritin and haptoglobin. But there is no significant difference in acute phase inflammatory proteins in healthy dipper when compared to healthy non dippers.

Keywords: acute phase inflammatory protein, h dippers, non-dippers, blood pressure, hypertension

INTRODUCTION

Hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg [1]. Cardiovascular disease is split into 2 stages. Stage one includes patients with pulsation vital sign 140-159 mmHg or pulse vital sign 90-99 mmHg. Stage 2 includes patients with systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg. In 2000, about 1billion people (26.4% of adults) were estimated to have hypertension worldwide, and there is a likelihood of increasing to more than 1.5billion by 2025 as a result of a high number of aging population in many developed countries and an increasing incidence of hypertension in developing ones. In Nigeria, it has approximately been estimated that about 35.2% of the population are suffering from hypertension [2]. Normal variation in blood pressure (BP) is characterized by a 10% to 20% reduction in BP from day to night [3]. Blood pressure shows a circadian rhythm. In healthy individuals, blood pressure reaches a peak in the morning hours and slowly falls during the day to reach the lowest levels in the night. Both systolic and diastolic blood pressures decrease by more than 10% during the night compared to the daytime.

The main determinant of the circadian variations of BP appears to be the activity of the sympathetic nervous system. However, several other neurohormonal systems regulating BP have been shown to follow a circadian rhythm and may contribute to the circadian variations in BP [4]. Acute phase proteins can be defined as those whose plasma protein concentration increase with inflammatory reaction (positive acute phase proteins). However, negative acute phase proteins are those whose plasma protein concentrations decrease with inflammatory reaction. Interleukin-(IL-) 6 is the major stimulator of the production of most acute-phase proteins. Acute phase proteins predict and/or reflect the intensity of cardiovascular diseases. Cardiovascular diseases are accompanied by the elevation of several positive acute phase reactants such as CRP, serum amyloid A (SAA), fibrinogen, white blood cell count, secretory nonpancreatic phospholipase 2-II (sPLA2-II), ferritin, and ceruloplasmin. Cardiovascular diseases are also accompanied by the reduction of negative acute phase reactants such as albumin, transferrin, transthyretin, retinol-binding protein, antithrombin, and transcortin. The concentration of acute phase reactants in plasma varies according to the severity of the cardiovascular disorder and also due to the differences of pattern of production of the individual protein. Cardiovascular diseases (CVDs) including hypertension are increasing globally. This increment has become a major concern in Africa countries such as Nigeria. In Nigeria, it has approximately been estimated that about 35.2% of the population are suffering from hypertension [2]. Cardiovacular parameters such as blood pressure, heart rate and coronary tonus change with the daily circadian rhythm [4]. The mechanism of diurnal blood pressure variation disorders is not clear. At night, the balance in the autonomous nervous system probably shifts towards the sympathetic nervous system [9]. If the blood pressure decrease is less than 10 to 20% during sleep, it is connected with target-organ damage. Particularly in non-dipper hypertensive patients, it is common to see left ventricular hypertrophy, congestive heart failure, myocardial infarction, stroke and renal failure (albuminuria and end-stage renal failure).

Recent studies suggest that acute phase proteins play a pivotal role in many aspects of cardiovascular diseases [8]. There have been speculations about the association of acute phase proteins with dippers and non dippers hypertensive patients, but the validation of such information have not been confirmed. Due to the paucity of information on the association of acute phase proteins in dipper and non dipper hypertensives with incident blood pressure, the present study is slated to determine the level of some essential acute phase proteins in dippers and non dippers hypertensives.

MATERIALS AND METHODS

Study Area

The study was carried out at the Federal Medical centre, Owerri, Imo state. Owerri is the capital city in Imo State and it consists of three Local Government Areas, with an estimated population of about 401,873 as of 2006 census and an approximately 100 square kilometres (40 sq mi) in area, Owerri is bordered by the Otamiri River to the east and the Nworie River to the south [10].

Study Population and Sample Size

Sample size determination

Sample size was determined in accordance to Araoye, [15]. From the sample size, approximately 25 individuals with incident blood pressure were selected from the subject population.

Selection Criteria

A. Inclusion criteria

The inclusion criteria are as follows:

(i) Patients newly diagnosed with hypertension

(ii) Subjects that gave consent to the study
(iii) Those with elevated blood pressure (≥140/90 mmHg)
(iv) Patients with no history of chronic viral infection, malignancy and/or liver diseases (HBV, HCV, HIV, and alcohol consumption)
(v) Subjects within the age of 30 to 60 years of age
(vi) Those who are not yet on drug regimen

B. Exclusion criteria

(i) Subjects that did not give the consent
(ii) Those hypertensive on drugs
(iii) Hypertensives below 30 and above 60 years of age
(iv) Chronic viral infections and/or liver diseases such as HBV, HCV, HIV, malignancy and alcoholism.

Study Design

This is a case control study involving a total of 50 subjects within the age range of 30 to 60 years. Twenty five (25) subjects are with incident blood pressure, while twenty five (25) are normotensive who served as control.The subjects daytime and nocturnal blood pressure were taken a day to the sample collection. Blood samples collected were used in the assay of acute phase proteins.

Sample Collection

Five milliliters (5 ml) of venous blood was collected and dispensed into a plain container. The tube was properly labeled with the subject's name, sample number and date of collection. The blood was allowed to clot at room temperature, and serum separated and harvested into a clean dry well labeled sample bottles following centrifugation at 3000 rpm for 5 minutes. The sample was stored in a freezer at -20^{oc}, prior to use.

Biochemical Parameters Determination

C-reactive protein, fibrinogen and serum haptogloblin was determined using ELISA techniques while serum ferritin was determined using immuno-turbidimetry method on the Hitachi 912 clinical analyzer.

Statistical Analysis

Results were presented in mean ± standard deviation (SD). All data obtained in the study were analyzed using student t-test (spss.21) and Pearson correlation coefficent. The level of significance was set at $p < 0.05$.

RESULTS

The mean systolic day blood pressure value was significantly increased (p=0.000) in dippers with incidenthypertension (153.82± 14.62) mmHg when compared to normotensive dippers (116.91± 7.20) mmHg. The mean diastolic day blood pressure value was significantly increased (p=0.000) in hypertensive subjects (94.73± 4.65) mmHg when compared to normotensive (75.36± 3.64) mmHg (Table 1). In table 2, the mean systolic night blood pressure value was significantly increased (p=0.009) in dippers with incidenthypertension (145.67± 11.46) mmHg when compared to normotensive dippers (116.36± 27.86) mmHg. The mean diastolic day blood pressure value was significantly increased (p=0.000) in dippers with incidenthypertension (95.20± 4.61) mmHg when compared to normotensive dippers (65.64±3.72) mmHg. Table 3 shows the mean systolic day blood pressure value was significantly increased (p=0.000) in non-dippers with incidenthypertension (165.11± 20.71) mmHg when compared to normotensive non-dippers (120.00± 4.76) mmHg. The mean diastolic day blood pressure value was significantly increased (p=0.000) in non-dippers with incidenthypertension (92.56± 6.00) mmHg when compared to normotensive non-dippers (73.60± 4.67) mmHg. In table 4, the mean systolic night blood pressure value was significantly increased (p=0.000) in dippers with incidenthypertension (161.22± 20.95mmHg when compared to normotensive dippers (114.50± 4.50) mmHg. The mean diastolic night blood pressure value was significantly increased (p=0.000) in dippers with incidenthypertension (88.33± 5.34) mmHg when compared to normotensive dippers (72.70± 3.80) mmHg. Table 5 shows that there was no significant difference (p=0.393) in the mean value of CRP in normotensive dipper subjects (1.94±0.60)mg/ml when compared to normotensive non dipper subjects (2.23±0.91)mg/ml. There was no significant difference (p=0.288) in the mean value of fibrinogen in normotensivedipper subjects (3.72±1.01)mmol/L when compared to normotensive non dipper subjects (4.19±0.94)mmol/L. There was no significant difference (p=0.116) in themean value of ferritin in normotensivedipper subjects (2.63±0.39)mg/L when compared to normotensive non dipper subjects (2.95±0.49)mg/L. There was no significant difference (0.419) in themean value of Haptoglobin in normotensivedipper subjects (1.17±0.28)g/L when compared to normotensive non dipper subjects (1.28±0.32)g/L. In table 6, the mean value of C-reactive protein was significantly reduced (p=0.002) in hypertensive dipper subjects (3.11±1.39)mg/ml when compared to hypertensive non dipper subjects (6.14±2.20)mg/ml.

The mean value of fibrinogen was significantly reduced (p=0.018) in hypertensive dipper subjects (5.32±1.11)mmol/L when compared to hypertensive non dipper subjects (7.04±1.71)mmol/L. There was no

significant difference (p=0.067) in themean value of ferritin in hypertensive dipper subjects (3.51±0.59)mg/L when compared to hypertensive non dipper subjects (4.13±0.78)mgl/L. There was no significant difference (0.239) in themean value of Haptoglobin in hypertensive dipper subjects (2.25±1.11)g/L when compared to hypertensive non dipper subjects (2.90±1.21)mgl/L.

Table 7 shows that the mean value of C-reactive protein was significantly increased (p=0.019) in hypertensive dipper subjects (3.11±1.39)mg/ml when compared to normotensivedipper subjects (1.94±0.60)mg/ml. The mean value of fibrinogen was significantly increased (p=0.003) in hypertensive dipper subjects (5.32±1.11)mmol/L when compared to normotensivedipper subjects (3.72±1.01)mmol/L. The mean value of ferritin was significantly increased (p=0.001) in hypertensive dipper subjects (3.51±0.59)mg/L when compared to normotensivedipper subjects (2.63±0.39)mg/L. The mean value of haptoglobin was significantly increased (p=0.006) in hypertensive dipper subjects (2.25±1.11)g/L when compared to normotensivedipper subjects (1.17±0.28)g/L.

In table 8, the mean value of C-reactive protein was significantly increased (p=0.000) in hypertensive non dipper subjects (6.14±2.20)mg/ml when compared to normotensivedipper subjects (2.23±0.91)mg/ml. The mean value of fibrinogen was significantly increased (p=0.000) in hypertensive non dipper subjects (7.04±1.71)mmol/L when compared to normotensivedipper subjects (3.72±1.01)mmol/L. The mean value of ferritin was significantly increased (p=0.001) in hypertensive non dipper subjects (4.13±0.78)mg/L when compared to normotensivedipper subjects (2.95±0.49)mg/L. The mean value of haptoglobin was significantly increased (p=0.001) in hypertensive dipper subjects (2.90±1.21)g/L when compared to normotensivedipper subjects (1.28±0.32)g/L.

Table 9 shows that there was a non-significant negative correlation (r=-0.03, p=0.933; r=-0.29, p=0.445 and r=-0.89, p=0.822) of C-reactive protein, fibrinogen and ferritin in hypertensive dippers with hypertensive non dippers. There was a non-significant positive correlation (r=0.53, p=0.139) of haptoglobin in hypertensive dippers with hypertensive non dippers.

Table 1: Mean Value of Day Blood Pressure in Dippers with Incident Hypertension

Parameter	Normotensive	Hypertensive	t-value	p-value
Systole (mmHg)	116.91± 7.20	153.82± 14.62	7.51	0.000
Diastole (mmHg)	75.36± 3.64	94.73± 4.65	10.88	0.000

Results are means and standard deviations, p<0.05 is statistically significant and p>0.05 is not statistically significant

Table 2: Mean Value of Night Blood Pressure in Dippers with Incident Hypertension

Parameter	Normotensive	Hypertensive	t-value	p-value
Systole (mmHg)	116.36± 27.86	145.67± 11.46	2.95	0.009
Diastole (mmHg)	65.64± 3.72	95.20± 4.61	16.23	0.000

Results are means and standard deviations, p<0.05 is statistically significant and p>0.05 is not statistically significant

Table 3: Mean Value of Day Blood Pressure in Non- Dippers with Incident Hypertension

Parameter	Normotensive	Hypertensive	t-value	p-value
Systole (mmHg)	120.00± 4.76	165.11± 20.71	7.04	0.000
Diastole (mmHg)	73.60± 4.67	92.56± 6.00	7.73	0.000

Results are means and standard deviations, p<0.05 is statistically significant and p>0.05 is not statistically significant

Table 4: Mean Value of Night Blood Pressure in Non- Dippers with Incident Hypertension

Parameter	Normotensive	Hypertensive	t-value	p-value
Systole (mmHg)	114.50± 4.50	161.22± 20.95	6.89	0.000
Diastole (mmHg)	72.70± 3.80	88.33± 5.34	7.41	0.000

Results are means and standard deviations, p<0.05 is statistically significant and p>0.05 is not statistically significant

Table 5: Mean Value of C-reactive protein, Fibrinogen, Ferritin and Haptoglobin in Normotensive Dipper Subjects

Parameter	Normotensive Dipper Subjects	Normotensive Non Dipper Subjects	t-value	p-value
C-reactive Protein (mg/ml)	1.94±0.60	2.23±0.91	0.87	0.393
Fibrinogen (mmol/L)	3.72±1.01	4.19±0.94	1.09	0.288
Ferritin (mg/L)	2.63±0.39	2.95±0.49	1.65	0.116
Haptoglobin (g/L)	1.17±0.28	1.28±0.32	0.83	0.419

Results are means and standard deviations, $p<0.05$ is statistically significant and $p>0.05$ is not statistically significant

Table 6: Mean Value of C-reactive protein, Fibrinogen, Ferritin and Haptoglobin in Hypertensive Dipper Subjects

Parameter	Hypertensive Dipper Subjects	Hypertensive Non Dipper Subjects	t-value	p-value
C-reactive Protein (mg/ml)	3.11±1.39	6.14±2.20	3.63	0.002
Fibrinogen (mmol/L)	5.32±1.11	7.04±1.71	2.63	0.018
Ferritin (mg/L)	3.51±0.59	4.13±0.78	1.96	0.067
Haptoglobin (g/L)	2.25±1.11	2.90±1.21	1.22	0.239

Results are means and standard deviations, $p<0.05$ is statistically significant and $p>0.05$ is not statistically significant

Table 7: Mean Value of C-reactive protein, Fibrinogen, Ferritin and Haptoglobin in Hypertensive Dipper Subjects Vs Normotensive Dipper Subjects

Parameter	Hypertensive Dipper Subjects	Normotensive Dipper Subjects (Control)	t-value	p-value
C-reactive Protein (mg/ml)	3.11±1.39	1.94±0.60	2.56	0.019
Fibrinogen (mmol/L)	5.32±1.11	3.72±1.01	3.47	0.003
Ferritin (mg/L)	3.51±0.59	2.63±0.39	4.04	0.001
Haptoglobin (g/L)	2.25±1.11	1.17±0.28	3.12	0.006

Results are means and standard deviations, $p<0.05$ is statistically significant and $p>0.05$ is not statistically significant

Table 8: Mean Value of C-reactive protein, Fibrinogen, Ferritin and Haptoglobin in Hypertensive Non Dipper Subjects Vs Normotensive Non Dipper Subjects

Parameter	Hypertensive Non Dipper Subjects	Normotensive Non Dipper Subjects (Control)	t-value	p-value
C-reactive Protein (mg/ml)	6.14±2.20	2.23±0.91	5.17	0.000
Fibrinogen (mmol/L)	7.04±1.71	4.19±0.94	4.57	0.000
Ferritin (mg/L)	4.13±0.78	2.95±0.49	3.98	0.001
Haptoglobin (g/L)	2.90±1.21	1.28±0.32	4.09	0.001

Results are means and standard deviations, $p<0.05$ is statistically significant and $p>0.05$ is not statistically significant.

Table 9: Correlation of Acute Phase Proteins in Hypertensive Dippers with Hypertensive Non Dippers

Variable	N	R	p-value
C-reactive protein	25	-0.03	0.933
Fibrinogen	25	-0.29	0.445
Ferritin	25	-0.89	0.822
Haptoglobin	25	0.53	0.139

$p<0.05$ is statistically significant; $p>0.05$ not statistically significant

DISCUSSION

Inflammatory status could play a role in alterations of blood pressure (BP) circadian rhythm [11]. It was observed in the current study that the mean value of systolic and diastolic blood pressure was significantly increased in hypertensive dippers and non dippers when compared with normotensive dippers and non dippers. The result clearly indicates that high blood pressure is associated with increase level of systolic and diastolic pressure. Elevation of extracellular fluid (ECF) increases the preload, which eventually contributes to the generation of hypertension which ultimately increases systolic pressure. Diastolic pressure also is determined by the systolic pressure in that an increase in systolic pressure leads to a higher starting point from which the arterial pressure may descend between contractions, this leads to a higher diastolic pressure starting point. The result is in agreement with the findings of Tang *et al.*, [12]. In the present study, the mean value of C-reactive protein was significantly increased in hypertensive dipper and non dipper subjects when compared to normotensive dipper and non dipper subjects respectively. C-reactive protein (CRP) is a pentaxin synthesized primarily in the liver in response to pro-inflammatory cytokines that is one of the best known markers of cardiovascular disease. C-reactive protein levels have been shown to predict the development of arterial heart diseases and were associated with endothelial dysfunction, atherosclerosis, CV events in hypertensive patients [14]. Although the exact mechanisms underlying the relationship between alteration of circadian rhythm of BP in hypertensive patients and development of cardiovascular events are unknown, the significant increase in C-reactive protein could be as a result of high blood pressure which could be attributed to inflammation. This study is in consistent with those from some other similar studies [13].

The study also reveals that the mean value of fibrinogen was significantly increased in hypertensive dipper subjects and non dipper subjects when compared to healthy dipper and non dipper subjects. The increase could be attributed to the fact that hypertension leads to an inflammatory response and fibrinogen is an acute phase reactant component of the coagulation cascade with a half-life of one week [17]. This is consistent with the study carried out by Agorasti*et al.*, [16]. The mean value of ferritin and haptoglobin was significantly increased in hypertensive dipper subjects and non dipper subjects when compared to healthy dipper and non dipper subjects. The increase could be attributed to the fact ferritin and haptoglobin are all inflammatory markers, since hypertension causes inflammation, there will be an increase in the level of ferritin and haptoglobin. Ferritin is a universal intracellular protein that stores iron and releases it in a controlled fashion. Haptoglobin functions to bind the free plasma hemoglobin, which allows degradative enzymes to gain access to the hemoglobin while at the same time preventing loss of iron through the kidneys and protecting the kidneys from damage by hemoglobin [18]. Thou, the mean value of C-reactive protein and fibrinogen was significantly reduced ($p<0.05$) in hypertensive dipper subjects when compared to hypertensive non dipper subjects. The exact mechanism behind the decrease is not clear, but a study carried out Lewington *et al.*, [11] reported that in hypertensive patients, the absence of a nocturnal blood pressure dipping has been associated with the development of target organ damage, which could have resulted in the increase of C-reactive protein and fibrinogen in hypertensive non dipper subjects. This result is in line with the study carried out by Lise *et al.*, [20].

There was no significant difference ($p>0.05$) in the mean value of ferritin and haptoglobin in hypertensive dipper subjects when compared to hypertensive non dipper subjects. Thou the reason behind in the insignificant difference is not clear, but one clear reason might be as a result that ferritin and haptoglobin are not active markers of inflammatory response, or that the patient screened were not badly affected by the high blood pressure. Medial hypertrophy is associated with considerable development of the extracellular matrix of the media and even the adventitia. These histopathologic changes result in reduced compliance, and distensibility of the arterial wall. Thus, the deterioration of aortic function may be an early predictor of coronary atherosclerosis and show end organ damage in non dippershypertensive subjects [19]. This is in line with the study carried out by Nakano*et al.*, [21], who in their study on the analysis of acute phase reactant proteins in hypertensives with circadian variation reported a similar result.

There was no significant difference ($p>0.05$) in the mean value of C-reactive protein, fibrinogen, ferritin and haptoglobin in healthy dipper subjects when compared to healthy non dipper subjects. This is a clear indication that normal blood pressure variation is not associated with increase acute phase protein levels. This is in line with the study carried out by Nakano *et al.*, [21].

There was a non-significant correlation between acute phase proteins in hypertensive dippers with hypertensive non dipper subjects. Even though there was some difference in the individual levels of acute phase proteins.

CONCLUSION

Non dipper variation in high blood pressure is associated with increase in C-reactive protein, fibrinogen, ferritin and haptoglobin. But there is no significant difference in acute phase inflammatory proteins in healthy dipper when compared to healthy non dippers. Although the individual variation in these parameters could be a case for further consideration. It is important that blood pressure level be carefully monitored in patients with metabolic syndrome to identify those with the non-dipper BP pattern and that such patients should be carefully followed and promptly treated to minimize aortic dysfunction risk.

CONSENT

All informed consent was sought from the subjects and adequate verbal information was obtained from the subjects, which enabled them to know the essence of collecting their blood samples and the nature of the research work. Anonymity was assured as names were not required at any stage of the study.

ETHICAL APPROVAL

Ethical approval of the study was obtained from Federal Medical Center Owerri, Nigeria.

COMPETING INTEREST

Authors have declared that no competing interest exists

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