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Association of Acute Phase Protein with Diurnal Variation of Blood Pressure among Post Menopausal Women with Hypertension

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ABSTRACT

This study was aimed at evaluating the association of acute phase protein with diurnal variation of blood pressure among healthy pre and post-menopausal women. The study population consisted of 40 postmenopausal women and premenopausal women (Control). Blood samples collected were used in the assay of acute phase proteins. C-reactive protein, fibrinogen, ferritin and haptoglobin was determined using standard laboratory procedures. All data obtained in the study were analyzed using student t-test (spss.21). The level of significance was set at $p < 0.05$. The mean value of systole was significantly increased (p=0.001) in Nornotensive menopausal women (126.30±6.63) mmHg when compared to normotensive premenopausal women (116.60±4.33) mmHg. The mean value of diastole was significantly increased (p=0.000) in normotensive menopausal women (77.20±5.51) mmHg when compared to normotensive premenopausal women (68.40±3.37) mmHg. The mean value of C-reactive protein was significantly increased (p=0.002) in normotensive menopausal women (3.04±0.74)ng/ml when compared to normotensive premenopausal women (1.99±0.55)ng/ml. The mean value of haptoglobin was significantly increased (p=0.037) in normotensive menopausal women (2.08±1.15)g/L when compared to normotensive premenopausal women (1.24±0.26)g/L. There was no significant difference (p=0.525) in the mean value of fibrinogen in normotensive menopausal women (3.53±0.87)nmol/L when compared to normotensive premenopausal women (3.81±1.02)nmol/L. There was no significant difference (p=0.299) in the mean value of ferritin in normotensive menopausal women (2.95±0.59)ng/L when compared to normotensive premenopausal women (2.69±0.48)ng/L. The mean value of C-reactive protein was significantly increased (p=0.000) in hypertensive menopausal women (4.31±0.85)ng/ml when compared to normotensive premenopausal women (1.99±0.55)ng/ml. The mean value of fibrinogen was significantly increased (p=0.038) in hypertensive menopausal women (4.89±1.13)nmol/L when compared to normotensive premenopausal women (3.81±1.02)g/L. The mean value of haptoglobin was significantly increased (p=0.000) in hypertensive menopausal women (2.95±1.24)gl/L when compared to normotensive premenopausal women (1.24±0.26)g/L. The mean value of ferritin was significantly increased (p=0.021) in hypertensive menopausal women (3.30±0.59)ng/L when compared to normotensive premenopausal women (2.69±0.48)ng/L. The mean value of C-reactive protein was significantly increased (p=0.002) in hypertensive menopausal women (4.31±0.85)ng/ml when compared to normotensive menopausal women (3.04±0.74)ng/ml. The mean value of fibrinogen was significantly increased (p=0.008) in hypertensive menopausal women (4.89±1.13)nmol/L when compared to normotensive menopausal women (3.53±0.87)mmol/L. There was no

significant difference (p=0.122) in the mean value of haptoglobin in hypertensive menopausal women (2.95±1.24)gl/L when compared to normotensive menopausal women (2.08±1.15)g/L. There was no significant difference (p=0.204) in the mean value of ferritin in hypertensive menopausal women (3.30±0.59)ngl/L when compared to normotensive menopausal women (2.95±0.59)ng/L. From the study, Menopausal women with high blood pressure presented with significant increase in C-reactive protein, fibrinogen, haptoglobin and ferritin.
Keywords: acute phase protein, diurnal variation, blood pressure, post-menopausal women, hypertension

INTRODUCTION

Hypertension is defined as having a blood pressure with higher of systolic and diastolic than 140 over 90 mm/Hg, with consensus across medical guidelines [1]. Blood pressure has a daily pattern, it is normally lower at night while you're sleeping and starts to rise a few hours before you wake up and continues to rise during the day, usually peaking in the middle of the afternoon, then in the late afternoon and evening, it begins dropping again [2]. Although a diurnal variation in blood pressure (BP) and heart rate (HR) has been recognized since 1914, recent reports of circadian variation in cardiovascular ischemic syndromes have suggested that there may be a link between the morning surge in blood pressure (BP) and heart rate (HR), and the increased risk of acute myocardial infarction, stroke, and sudden cardiac death during the early morning hours [3]. Acute phase proteins can be defined as those whose plasma protein concentration increases with inflammatory reaction (positive acute phase proteins) [2]. 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 high blood pressure [4]. Cardiovascular diseases are accompanied by the elevation of several positive acute phase reactants such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, white blood cell count, secretory nonpancreatic phospholipase 2-II (sPLA2- II), ferritin, and ceruloplasmin [3]. 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 [4].

C-reactive protein is a plasma protein involved in the acute-phase response and is synthesized primarily by the liver in response to the presence of interleukin 1 and 6. It usually is present in minute quantities in human serum but may increase 100–1000-fold within 72 h of tissue injury [5]. CRP was hypothesized to increase the risk of developing hypertension, which has been corroborated by studies among individuals with hypertension. Menopause occurs when a woman hasn't menstruated in 12 consecutive months and can no longer become pregnant naturally. It usually begins between the ages of 45 and 55, but can develop before or after this age range. Most women first begin developing menopause symptoms about four years before their last period. Symptoms often continue until about four years after a woman's last period [6].

Hypertension in women is often undiagnosed or inadequately treated, especially after menopause when cardiovascular risk increases. In premenopausal women, endogenous estrogens maintain vasodilation and thus contribute to blood pressure control. Aging and the loss of endogenous estrogen production after menopause are accompanied by increases in blood pressure, contributing to the high prevalence of hypertension in older women [8]. About one percent of women begin menopause before the age of 40, which is called premature menopause or primary ovarian insufficiency. About 5 percent of women undergo menopause between the ages of 40 and 45. This is referred to as early menopause. [7]. During perimenopause, menstrual periods become irregular. Periods may be late, or may completely skip one or more periods. Menstrual flow may also become heavier or lighter. Menopause is defined as a lack of menstruation for one full year. Post menopause refers to the years after menopause has occurred. Cross-sectional studies suggest a relationship between menopause and both hypertension and acute phase protein. High blood pressure is the commonest cause of death in women in Nigeria. Hypertension is rare in premenopausal women compared with men of similar age, whereas its incidence increases in menopausal women, suggesting a protective effect of endogenous estrogen [9]. This risk may be partly attributed to adverse changes in endothelial function and inflammation that occur early in the postmenopausal period and could lead to the acceleration of high blood pressure. Menopause has been implicated as a unique cardiovascular disease (CVD) risk factor in women, therefore, it is important to determine if changes in the predominance of risk factors such as inflammation that occur during the menopausal transition could affect the prevalence of hypertension. Due to the paucity of information on

the level of acute phase proteins with diurnal variation in blood pressure among pre and post-menopausal women, the present study is aimed at evaluating the association of acute phase proteins to the dippers and non-dippers blood pressure profile as an indicator for prognostic outcome.

MATERIALS AND METHODS

Study Area

The study was conducted in Owerri, Imo State. Owerri is located in the Eastern part of Nigeria between longitude 6^0 50' E and 7^0 25' E and between latitude 445 and 715 N of the equator with an area of about 5100sq km. It is bordered by Abia state to the North and River Niger and Delta on the West by Anambra state to the North and Rivers state to the south. It provides home for a population of 1,261,213 people of mainly Igbo ethnic group and a few other tribes. This population is made up of 620,990 males and 640,223 females (NPC, 2006).

Study Population

The study population consisted of 40 postmenopausal women and premenopausal women (Control) The study population consisted predominantly women within the ages of 18 years and 60years recruited within and outside the University community. Ethical approval of the study was obtained from Federal Medical Center Owerri, Nigeria. The consents of the volunteer subjects were duly sort. Each subject signed an informed consent form after which the procedure and implication were explained using a language the subjects would understand.

Sample size determination: Araoye, [12] formula for calculating sample size was used in this study.

Selection Criteria

Inclusion criteria

The inclusion criteria are as follows:

i. Women within the age of 18 years and 60 years that have stop menstruating for a year.
ii. Women not sick of hypertension or any other cardiovascular disease.
iii. Subjects with no history of chronic viral infection and/or liver diseases (HBV, HCV, HIV, and alcohol consumption)
iv. Those who are not on long-term drug regimen
v. Subjects whose informed consent was obtained

Exclusion criteria

i. Women who are below 18 and above 60 years.
ii. Subjects whose informed consent was not obtained
iii. Subject with Chronic viral infections and/or liver diseases such as HBV, HCV, HIV, and alcoholism.
iv. Those who are on long-term drug regimen.

Study Design

A cross-sectional study was conducted within the month of June to August 2021 and all eligible women who filled the questionnaire and gave a written informed consent for the study period were sampled.A total of 40 female subjects participated in the study. The study was grouped in two, group A representing (20) normotensive premenopausal women, group B represents twenty (20) normotensive menopausal women, while group C represents twenty (20) hypertensive menopausal women.

Sample Collection

Blood samples were collected aseptically by vein puncture, using a 5ml sterile disposable syringes and needles from petroleum attendants and non-petroleum attendants and was disposed into a labelled plain dry specimen container. The samples were centrifuged at 3,000rpm for 5 minutes to separate and to obtain the serum. The serum were extracted using a pipette and was introduced into another specimen container, and stored at -20^{oc} until required.

Biochemical Parameters Determination

All reagents used were commercially prepared and procured and the manufacturer's standard operating procedures were strictly followed. C-reactive protein (CRP) was determined using the latex-enhanced nephelometry technique, fibrinogen and haptogloblin was determined using ELISA method. Serum ferritin was estimated using the immuno-turbidimetry method, the Hitachi 912 clinical analyzer (Roche kits) was employed.

Statistical Analysis

Data was analyzed using software statistical package for social sciences (SPSS) version 20.0 the results were expressed as mean and standard deviation (mean ± Difference in mean values between groups were assessed by student t-test. Tests with a probability value of $P< 0.05$ was considered statistically significant.

RESULTS

Table 1 shows that the mean value of systole was significantly increased (p=0.000) in hypertensive menopausal women (156.90±14.53) mmHg when compared to normotensive menopausal women (126.30±6.63) mmHg. The mean value of diastole was significantly increased (p=0.000) in menopausal women (94.00±8.03) mmHg when compared to normotensive menopausal women (77.20±5.51) mmHg. The mean value of C-reactive protein was significantly increased (p=0.002) in hypertensive menopausal women (4.31±0.85)ng/ml when compared to normotensive menopausal women (3.04±0.74)ng/ml. The mean value of fibrinogen was significantly increased (p=0.008) in hypertensive menopausal women (4.89±1.13)nmol/L when compared to normotensive menopausal women (3.53±0.87)mmol/L. There was no significant difference (p=0.122) in the mean value of haptoglobin in hypertensive menopausal women (2.95±1.24)gl/L when compared to normotensive menopausal women (2.08±1.15)g/L. There was no significant difference (p=0.204) in the mean value of ferritin in hypertensive menopausal women (3.30±0.59)ngl/L when compared to normotensive menopausal women (2.95±0.59)ng/L.

In table 2, the mean value of systole was significantly increased (p=0.000) in hypertensive menopausal women (156.90±14.53) mmHg when compared to normotensive premenopausal women (116.60±4.33) mmHg. The mean value of diastole was significantly increased (p=0.000) in menopausal women (94.00±8.03) mmHg when compared to normotensive premenopausal women (68.40±3.37) mmHg. The mean value of C-reactive protein was significantly increased (p=0.000) in hypertensive menopausal women (4.31±0.85)ng/ml when compared to normotensive premenopausal women (1.99±0.55)ng/ml. The mean value of fibrinogen was significantly increased (p=0.038) in hypertensive menopausal women (4.89±1.13)nmol/L when compared to normotensive premenopausal women (3.81±1.02)g/L. The mean value of haptoglobin was significantly increased (p=0.000) in hypertensive menopausal women (2.95±1.24)gl/L when compared to normotensive premenopausal women (1.24±0.26)g/L. The mean value of ferritin was significantly increased (p=0.021) in hypertensive menopausal women (3.30±0.59)ng/L when compared to normotensive premenopausal women (2.69±0.48)ng/L.

Table 3 shows that the mean value of systole was significantly increased (p=0.001) in normotensive menopausal women (126.30±6.63) mmHg when compared to normotensive premenopausal women (116.60±4.33) mmHg. The mean value of diastole was significantly increased (p=0.000) in normotensive menopausal women (77.20±5.51) mmHg when compared to normotensive premenopausal women (68.40±3.37) mmHg. The mean value of C-reactive protein was significantly increased (p=0.002) in normotensive menopausal women (3.04±0.74)ng/ml when compared to normotensive premenopausal women (1.99±0.55)ng/ml. The mean value of haptoglobin was significantly increased (p=0.037) in normotensive menopausal women (2.08±1.15)g/L when compared to normotensive premenopausal women (1.24±0.26)g/L. There was no significant difference (p=0.525) in the mean value of fibrinogen in normotensive menopausal women (3.53±0.87)nmol/L when compared to normotensive premenopausal women (3.81±1.02)nmol/L. There was no significant difference (p=0.299) in the mean value of ferritin in normotensive menopausal women (2.95±0.59)ng/L when compared to normotensive premenopausal women (2.69±0.48)ng/L. [2-3]

Table 1: Mean Value of Systole, Diastole, C-reactive Protein, Fibrinogen, Haptoglobin and Ferritin in Hypertensive Menopausal Women and Normotensive Menopausal Women

Parameter	Hypertensive Menopausal	Normotensive Menopausal	t-value	p-value
Systole (mmHg)	156.90±14.53	126.30±6.63	6.06	0.000
Diastole (mmHg)	94.00±8.03	77.20±5.51	5.45	0.000
C-reactive Protein (ng/ml)	4.31±0.85	3.04±0.74	3.56	0.002
Fibrinogen (nmol/L)	4.89±1.13	3.53±0.87	2.99	0.008
Haptoglobin (g/L)	2.95±1.24	2.08±1.15	1.62	0.122
Ferritin (ng/L)	3.30±0.59	2.95±0.59	1.32	0.204

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

Table 2: Mean Value of Systole, Diastole, C-reactive Protein, Fibrinogen, Haptoglobin and Ferritin in Hypertensive Menopausal Women Vs Normotensive Premenopaausal Women

Parameter	Hypertensive Menopausal	Normotensive Premenopausal	t-value	p-value
Systole (mmHg)	156.90±14.53	116.60±4.33	8.41	0.000
Diastole (mmHg)	94.00±8.03	68.40±3.37	9.29	0.000
C-reactive Protein (ng/ml)	4.31±0.85	1.99±0.55	7.22	0.000
Fibrinogen (nmol/L)	4.89±1.13	3.81±1.02	2.24	0.038
Haptoglobin (g/L)	2.95±1.24	1.24±0.26	4.26	0.000
Ferritin (ng/L)	3.30±0.59	2.69±0.48	2.53	0.021

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

Table 3: Mean Value of Systole, Diastole, C-reactive Protein, Fibrinogen, Haptoglobin and Ferritin in Normotensive Menopausal Women and Premenopaausal Women

Parameter	Menopausal	Premenopausal	t-value	p-value
Systole (mmHg)	126.30±6.63	116.60±4.33	3.87	0.001
Diastole (mmHg)	77.20±5.51	68.40±3.37	4.31	0.000
C-reactive Protein (ng/ml)	3.04±0.74	1.99±0.55	3.56	0.002
Fibrinogen (nmol/L)	3.53±0.87	3.81±1.02	0.65	0.525
Haptoglobin (g/L)	2.08±1.15	1.24±0.26	2.25	0.037
Ferritin (ng/L)	2.95±0.59	2.69±0.48	1.07	0.299

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

DISCUSSION

In the present study, the mean value of systolic and diastolic value was significantly increased in normotensive and hypertensive menopausal women when compared to normotensive premenopausal women. In premenopausal women, endogenous estrogens maintain vasodilation and thus contribute to blood pressure control. Aging and the loss of endogenous estrogen production after menopause are accompanied by increases in blood pressure, contributing to the high prevalence of hypertension in older women [16]. The result of this research is in agreement with the study carried out by Hage *et al.*, [17], who stated that in addition to the effect of estrogen on blood pressure control in women, high prevalence of obesity, lack of regular physical exercise, and dietary salt are also important factors contributing to, and aggravating postmenopausal hypertension. A similar study carried out by Dubey *et al.*, [18] also reported that during the menstrual cycle, blood pressure levels are inversely related to circulating estrogen

concentrations and lower when 17β-estradiol levels peak, reflecting the vasodilator activity of endogenous 17β-estradiol [19]. Similarly, increases of endogenous estrogen production during pregnancy contribute to maintenance of normotension despite marked increases in plasma volume and cardiac output [20]. The first decade after menopause is accompanied by an increase in blood pressure. The role of endogenous estrogens in the pathogenesis of hypertension is complex. Indeed, the effects of hormonal changes after menopause are often masked by the presence of other cardiovascular risk factors, eg, vascular aging, arterial stiffening, obesity, age-dependent changes in insulin sensitivity, and dyslipidemia [21].

It was observed from the result of the current study that the mean value of C-reactive protein was significantly increased ($p<0.05$) in normotensive and hypertensive menopausal women when compared to normotensive premenopausal. There was also a marked increase in C-reactive protein hypertensive menopausal women when compared to normotensive menopausal women. Inflammation is a complex process involving multiple cell types and secreted factors many of which have been implicated in hypertension, Inflammation, obesity and loss of endogenous estrogens are some of the mechanisms that have been implicated in the development of postmenopausal hypertension [22]. C-reactive protein contributes to development of hypertension by decreasing the production of nitric oxide from endothelial cells which results in vaso-dysregulation and endothelial dysfunction [15], upregulating angiotensin II subtype 1 (AT1) receptors which leads to activation of the renin-angiotensin-aldosterone systems (RAAS) and proliferation of vascular smooth muscle cells and induction of plasminogen activator inhibitor 1 activity [15]. The result of this study is in agreement with the report by 10 who stated that menopause is associated with increases in C-reactive protein.

There was no marked significant difference in fibrinogen level in normotensive menopausal women when compared with normotensive premenopausal women, but there was a significant increase in fibrinogen level in hypertensive menopausal women when compared to normotensive menopausal women. The increase in fibrinogen level as reported in this study is a clear indication that there exist a relationship between menopause and hypertension in women. The marked increase in fibrinogen level in hypertensive menopausal women could be as a result of increase in shear stress, endothelial dysfunction, and progressive vascular disease due to severe hypertension. Previous cross-sectional epidemiological studies reported a positive association between plasma fibrinogen level and elevated BP in menopausal women. A similar study carried out by Folsom, [23] suggested that these increase in fibrinogen in menopausal women with high blood pressure are less likely to be because of chance.

In this study, the mean value of haptoglobin was significantly increased ($p<0.05$) in normotensive and hypertensive menopausal women when compared to normotensive premenopausal women. Several reports has it that inflammation can increase during menopause due to declining estrogen level, haptoglobin is an acute phase reactant which plasma levels are increased during inflammation [24], so it is likely to say that menopause causes an increase in haptoglobin level. The result is in agreement with the findings of Chiellini *et al.*, [25] who stated that serum haptoglobin level was previously shown to be positively associated with decline in estrogen level. There was a no significant difference between haptoglobin level in hypertensive menopausal women when compared to normotensive menopausal women. The result of this finding gives a clear indication that increase in haptoglobin level is not associated with hypertension.

There was no significant difference ($p>0.05$) in the mean value of ferritin in normotensive menopausal women when compared to normotensive premenopausal women, but there was a significant difference ($p<0.05$) in the mean value of ferritin in hypertensive menopausal women when compared to normotensive premenopausal women. There is insufficient evidence to explain the underlying mechanism. There are several possible mechanisms about the association between serum ferritin levels and hypertension. One of which includes the development of atherosclerosis by elevated ferritin levels. Ferritin is a ubiquitous intracellular protein that is the key to controlling iron homeostasis and is a widely used biomarker for the diagnosis of iron deficiency [26]. Serum ferritin concentrations reflect not only body iron stores but also systemic inflammation. Inadequately elevated body iron as oxidative stress can convert less reactive free radicals to more reactive hydroxyl radicals. Elevated body iron can also cause damage to cellular membranes, lipids, proteins, and deoxyribonucleic acid (DNA) [11]. Elevation of ferritin causes oxidative stress, which leads to inflammation, endothelial damage and consequently atherosclerosis. Atherosclerosis process follows after, and then risk of hypertension can be increased. Experimental studies have shown that hypertension is associated with oxidative stress that can contribute to endothelial dysfunction and leads to BP elevation [13. The

result of this study is in agreement with the study carried out by Ryoo *et al*., [14], in their study, they reported significant associations between hypertension and serum ferritin level in menopausal women.

CONCLUSION

Menopause is associated with increase in systolic, diastolic, C-reactive protein and haptoglobin, there is no association between menopause and ferritin level. Menopausal women with high blood pressure presented with significant increase in C-reactive protein, fibrinogen, haptoglobin and ferritin. Increase in acute phase protein causes oxidative stress, which leads to inflammation, endothelial damage and increase risk of hypertension. It important that levels of C-reactive protein, fibrinogen, haptoglobin and ferritin should be determined in menopausal women presenting signs of high blood pressure.

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

The ethical clearance to conduct this study was appropriately obtained from the research and ethical committee of Faculty of health Sciences and College Ethical committee, Imo state University, Owerri, Nigeria.

COMPETING INTEREST

Authors have declared that no competing interest exists

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