Original Research Article

ANTIOXIDANTS AND BIOMARKERS OF INFLAMMATION AS RISK FACTORS OF VASCULAR COGNITIVE IMPAIRMENT IN ADULT HYPERTENSIVES

ABSTRACT

Aims: To examine if the antioxidants and biomarkers of inflammation are risk factors of vascular cognitive impairment in adult hypertensives is controversial among Nigerians

Study design: A total of 216 normoglycaemic individuals (aged 40-75 years) were enrolled into this study by convenient sampling method, and semi-structured questionnaire was used for the study.

Place and Duration of Study: Sample: Department of Chemical Pathology, Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, January 2019 and Nov 2019

Methodology: Data was analyzed using the Statistical Package for Social Sciences (SPSS) software 17.0 version. Analysis of variance (ANOVA) to test significance of variations, and Chi square analysis for determination of associations between variables. Two tailed t-test of significance at 95% confidence limit with $p<0.05$.

Sample: They included 81 Newly Diagnosed Hypertensives (NDH) without cognitive impairment, 69 Newly Diagnosed Hypertensives with Cognitive Impairment (NDHCI) and 66 healthy individuals (Controls).

Results: The SBP, DBP and BMI were higher in NDH and NDHCI than control while, height and HC were higher in NDHCI than NDH and control ($p<.02$). HDLC was lower in NDH and NDHCI than control ($p<.01$). In the NDH group, hs-CRP, SOD had a significantly positive relationship with SBP (β=225.22; β=.843) respectively while WC, HC and WHR had a significantly positive relationship with DBP (β=12.315; β=12.241; β=496.374. In control, hs-CRP, catalase and GSH had positive relationship with SBP (β=118.557; β=.024; β=.347) respectively. Height and HC had positive while WHR (in NDH) had inverse relationships with cognitive score (R^2=.139, 0.186, 0.306, 0.119; β =11.863, .493) respectively.

Conclusion: It was discovered that there was increase in inflammatory biomarkers, impairment in cognition, attention involving memory loss characterize and vascular cognitive impairment, with decrease in antioxidants facilitates progression of hypertension to cognitive impairment in Nigerian hypertensive.

Keywords: Antioxidants, Biomarkers, Vascular Cognitive Impairment and Hypertensive.

1. INTRODUCTION

Dementia, characterized by significant irreversible decline in cognitive function that is sufficiently severe to impair independent social and occupational activities is a feared geriatric condition that has become a growing public health problem worldwide. The World Health Organization Mental Health Gap (mhGAP) considers dementia a priority mental health disorder earmarked for scaled-up action on account of its huge economic cost and social burden (WHO 2019; WHO mental health forum, 2019). The Prevalence of dementia increases with increasing age, doubling every 5-year increase after age 65(CDC, 2019). Impairment in cognition plays central role in the onset of dementia (1).

Vascular cognitive impairment (VCI) is a spectrum of neurodegenerative disorders that is associated with cerebrovascular diseases (2). It is linked to damages to the vascular system, especially abnormalities of the arteries and vessels supplying the head region, which lead to progressive decline in thinking abilities (3). Cognitive function plays a central role in determining the well being and quality of life of adults as they pass from midlife to older ages, including their decisions to work, retire and spend or save their money. It is a concept that in its early stage creates an opportunity for preventive strategies for the onset of dementia (4). VCI is characterized by a specific cognitive profile involving preserved memory with impairments in attention and executive functioning, which includes planning, task flexibility and problem solving, daily activities is not necessarily impaired (5). Impairment of cognition as a result of elevated blood pressure has been associated with memory loss and other cognitive deficits like dementia and Alzheimers disease(6).

Hypertension has devastating effects on the brain; it is the major cause of stroke and a leading cause of dementia (7). It alters the structure of cerebral blood vessels and disrupts intricate vasoregulatory mechanism that assures an adequate blood supply to the brain. These alterations threaten the cerebral blood supply and increase the susceptibility of the brain to ischemic injury as well as reduced cognitive function. Across all WHO regions, including the Americas, Africa has the highest prevalence of hypertension where 46% of the entire population, 25 years of age and older is estimated to be hypertensive compared to 35 to 40% elsewhere in the world (WHO, 2019). Nigeria, the most populous country in the African continent, has an alarming record of hypertension with an

overall prevalence of 28.9% (Men-29.5%, women-25.0%). Many hypertensive Africans are unaware of their status, and are rarely treated or poorly controlled, making them at high risk for stroke, cognitive dysfunction, heart and renal disease (8). Demonstrated significant hypertension among traders in Ibadan, who were unaware of the disease (9).

According to the global burden of diseases study (GBD), 2016, hypertension is the most prominent non-communicable diseases that have great impact on cardiovascular outcomes. Hypertension related diseases (specifically ischemic heart diseases and cerebrovascular disease) are the top two leading causes of disability adjusted life years (DALYs) and years of life lost (YLL) globally. Hypertension may lead to cognitive impairment through several pathogenic factors; Gray matter loss as a result of micro vascular dysfunction induced by hypertension, loss of connectivity and network efficiency from white matter lesions, reduced perivascular clearance and neurovascular dysfunction. All these anomalies may be linked to hypertension via large artery stiffening thereby increases pulsatility in microvessels, which has been proposed to alter perivascular spaces. The enlarged and distorted perivascular spaces cause an alteration that could inhibit the disposal of potentially toxic by-products of brain activity; amyloid-β, which may eventually instigate oxidative stress and inflammation. The possible role of inflammation and oxidative stress in the development of cognitive dysfunction among Nigerian hypertensive patients are unclear and are therefore investigated in this study.

2. MATERIALS AND METHODS

Study Population

Two hundred and sixty participants were enrolled into this study. Thirty eight were excluded for the following pre-specified reasons: unwillingness to participate in the study (n = 10), dementia and Alzheimer disease (diagnosed by a neurologist; n = 4), Pre hypertensive (SBP between 120 and 140/ DBP between 80 and 90 =18), diabetes mellitus patients (FBS>126 on more than two

occasions); n = 12). Two hundred and sixteen participants aged 40-75 years thus, constituted the study population.

Participants with Hypertension: These were participants enrolled using the guidelines of the 7th Joint National Committee on hypertension (JNC 7, 2012). Diagnosis of hypertension; Pre-hypertension: Systolic blood pressure=120 – 139 and diastolic blood pressure 80 – 89. Stage I hypertension: Systolic blood pressure=140 – 159 and diastolic blood pressure 90 -99. Stage 2 hypertension: Systolic blood pressure: ≥160, Diastolic blood Pressure: ≥100. Eighty one (81) newly diagnosed hypertensive's age 40-75years that have systolic blood pressure of ≥140 and diastolic blood pressure ≥90 were enrolled into this study.

Participants with hypertension and cognitive impairment: Diagnosis of hypertensives with cognitive impairment, these participants were recruited based on the guidelines of the 7th joint National committee on hypertension (JNC 7) and community screening instrument on dementia (CSI-D). The CSI-D provides a global score of cognitive ability that correlates with function in activities of daily living. CSI-D measures various domains of cognitive function including orientation to time and place, registration, concentration, short-term recall, naming familiar items, repeating a common expression. It also makes provision for those that can neither read nor able to write. Two hundred and sixteen (216) participants' aged 40-75 years, were diagnosed using CSI-D by consultant neurologist at Medical Outpatients Department of the University College Hospital (UCH) Ibadan. The CSI-D was validated by the systematic mini mental state examination (SMMSE) instrument that is recognized internationally.

Controls: Sixty-six (66) apparently healthy participants with normal blood pressure and intact cognitive function were certified and enrolled by the same neurologist that diagnosed the cases for enrollment.

Inclusion Criteria for Hypertensive Participants.

Participants were recruited based on the 7th joint National committee on hypertension (JNC 7) criteria, without medication (lipid lowering drugs, antihypertensive drugs), between age 40 and 75years, non family history of vascular cognitive impairment, non diabetics, without stroke

Inclusion Criteria for the Hypertensive with Cognitive impairment

These were participants enrolled based on the 7th joint National committee on hypertension (JNC 7) and community screening instrument on dementia (CSI-D) criterium. They were newly diagnosed, not on medication, age between 40 and 75years.

Inclusion Criteria for Control

They were apparently healthy participants, enrolled after thorough medical examination and were found to be normotensive, intact cognition, aged between 40 and 75years, not on medication.

Sample Collection

Ten (10 mLs) of venous blood sample was collected asceptically from the participants after an overnight fasting by venepuncture. This was done by applying a tourniquet 4-6 inches (10- 15 cm) above the intended puncture site to obstruct the return of venous blood to the heart and to the distended vein. The site of the puncture, the media cubital vein in the antecubital fossa was first cleansed with alcohol swab, blood was then collected with new disposable pyrogen free needles and syringes after the skin had dried. Six milliliters (6mL) of blood was dispensed into plain bottle kept for 1hour to clot to obtain serum for the analysis of biomarkers of inflammation (Interleukin-6, High sensitivity C-reactive protein) and 2mL into lithium heparin bottle for the Albumin estimation. The remaining 2mL was dispensed into fluoride oxalate bottle for plasma glucose estimation within two weeks. All bottles were labeled appropriately and centrifuged at 500g for five minutes after which serum and plasma were extracted and stored in small aliquots at -20^0C until analysis was done. Fasting blood (10mL) was collected from each participant for biochemical analyses. Albumin, glucose and inflammatory markers {Interleukin-6 (IL-6) and High Sensitivity C- Reactive Protein (hs-CRP)] in serum were estimated by ELISA.

Demographic Indices

Semi structured pretest questionnaire was completed by each subject in order to obtain demographic data which include; gender, age, smoking history, alcohol consumption, family history

of hypertension, cognitive impairment, drug and dietary history presence of undiagnosed diabetes, chronic kidney disease, educational status, marital status, occupation and life style.

BLOOD PRESSURE MEASUREMENTS

BP measurements were performed using a mercury sphygmomanometer. Adequately sized cuffs (standard cuff of 23 × 12 cm / a large cuff of 34 × 15 cm) according to arm circumference were placed on the non-dominant arm. The first and fifth phases of Korotkoff sounds were taken as the systolic and diastolic BP, respectively. The measurements were taken after the patients had rested for 10 min in the sitting position, rested their back, legs resting on the ground (not crossed), empty their bladder, with the arm comfortably placed at the heart level. Two measurements were taken at 2-min intervals. The mean of the set of two measurements was calculated to give the systolic and diastolic BPs. Clinical hypertension was defined as a BP ≥140/90 mm Hg.

MEASUREMENT OF COGNITIVE FUNCTION

The Community screening instrument for dementia (CSID) was used to assess cognitive function and results in a score of 30 (unimpaired) to 0 (impaired). It provides a global score of cognitive ability that correlates with function in activities of daily living. The CSID measures various domains of cognitive function including orientation to time and place, registration, concentration, short-term recall, naming familiar items, repeating a common expression construct a diagram, and follow a three-step verbal command. It provides opportunity for those that cannot read and write, provides a baseline score of cognitive function and pinpoints specific deficits that can aid in forming a diagnosis. The CSID was validated using the systematic minimental state examination instrument. The Systematic mini mental state examination (SMMSE) is a reliable instrument that allows practitioners to accurately measure cognitive deficits and deterioration over time and it is recognized internationally.

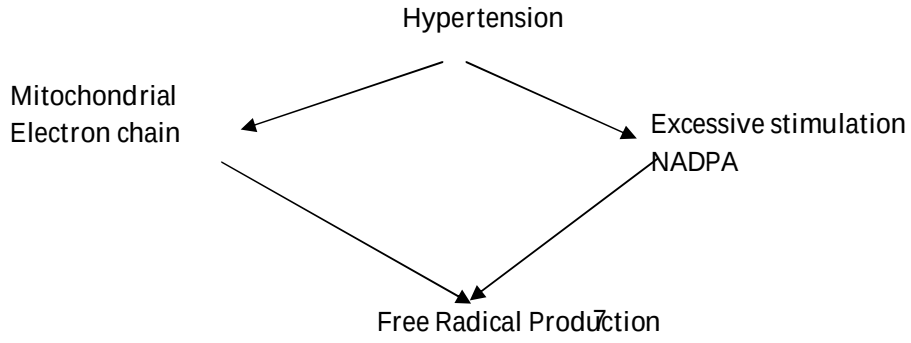
STATISTICAL ANALYSIS

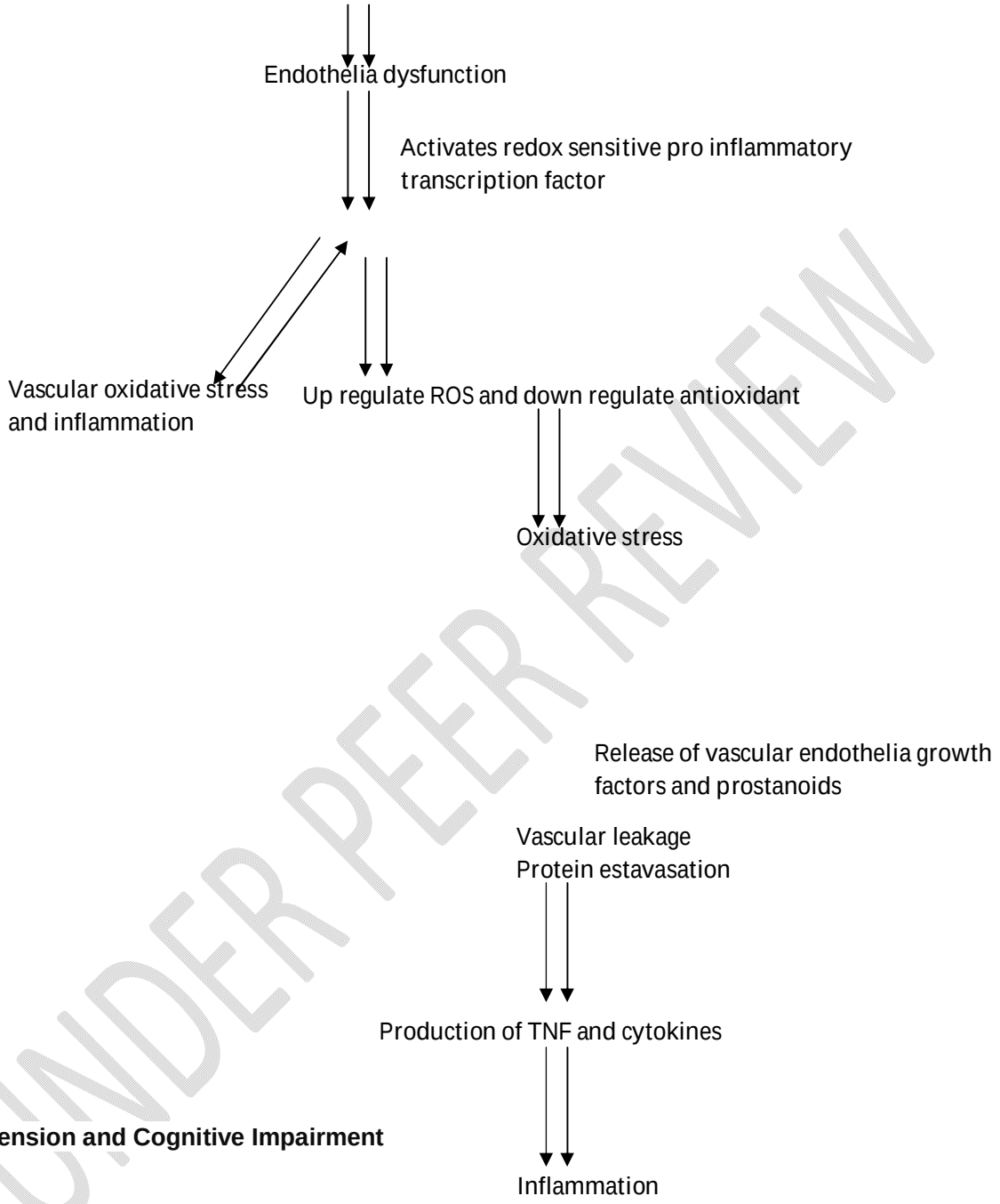
Data from the study population were collected and analyzed using the Statistical Package for Social Sciences (SPSS) software 17.0 version (SPP Inc., Richmond, CA).

For quantitative variables: Analysis of variance (ANOVA) was used to test significance of variations and Post Hoc was used for comparison of multiple variables. Linear regression analysis was employed to determine relationship between variables.

For non quantitative variables: Chi square analysis was used for determination of associations between variables. Two tailed t-test of significance at 95% confidence limit with $p<0.05$.

Fig 1: COGNITIVE DYSFUNCTION IN HYPERTENSION: THE ROLE OF OXIDATIVE STRESS AND INFLAMMATION.





Hypertension and Cognitive Impairment

The SBP, DBP were higher in NDH and NDHCI than control ($p<0.02$), which suggests that hypertension is not the only contributor to cognitive decline. No significant relationship was observed between blood pressure and cognitive impairment in this study. Cognitive impairment may be present irrespective of blood pressure readings in hypertensives contrary to recent reports by (10)

The associations of marital status, occupation, alcohol intake and type of symptoms of hypertension were significantly different among NDH, NDHCI and control ($p<0.05$). Marriage was associated with hypertension and cognitive impairment in this study. Contrarily, (10) reported that being single or widowed was associated with higher odds of cognitive impairment compared with being married. Predominantly manual occupation throughout life has increased risk of cognitive impairment compared with those with higher intellectual requirements (11)**.** Heavy alcohol intake adversely affects the brain through neurotoxic and pro-inflammatory effects as well as micronutrient deficiency (12). More of the NDH than other groups did not havesymptoms of hypertension. (14) demonstrated significant hypertension among traders in Ibadan, who were unaware of the disease.

3. RESULTS & DISCUSSION

Table1: Neuropsychological Assessment in Hypertensives, Hypertensives with congnitive impairment and control.

Cognitive Domains	Response	NDH n=81 (%)	NDHCI n=69 (%)	C n=66 (%)	X^2	P
Reg. of name	Yes	72(88.9)	41(62.1)	66(100.0)	37.6	0.001*
	No	9(11.1)	25(37.9)	0(0.0)		
Language Expression	Yes	63(77.8)	38(57.6)	66(100.0)	35.1	0.001*
	No	18(22.2)	28(42.4)	0(0.0)		
Defintion of Terms	Yes	57(70.8)	20(30.3)	66(100.0)	73.3	0.001*
	No	24(29.6)	46(69.7)	0(0.0)		

Memory Recall	Yes	52(64.2)	8(12.1)	65(98.5)	103.2	0.001*
	No	29(35.8)	58(87.9)	1(1.5)		
Attention to Calculation	Yes	43(53.1)	5(7.6)	64(97.0)	105.8	<0.001*
	No	38(46.9)	61(82.4)	2(3.0)		
Orientation to Place	Yes	72(88.9)	3(4.5)	66(100.0)	164.5	0.000*
	No	9(11.1)	63(95.5)	0(0.0)		
Orientation to Time	Yes	56(69.1)	5(7.6)	64(97.0)	114.7	<0.001*
	No	25(30.9)	61(92.4)	2(3.0)		
Motor Response	Yes	70(86.4)	16(24.2)	66(100.0)	107.2	<0.001*
	No	11(13.6)	50(75.8)	0(0.0)		
Memory Short Story	Yes	55(67.9)	4(6.1)	66(100.0)	124.7	<0.001*
	No	26(32.1)	62(93.9)	0(0.0)		
Semantic Memory	Yes	49(60.5)	2(3.0)	65(98.5)	123.2	<0.001*
	No	32(39.5)	64(97.0)	1(1.5)		
Stick Design assessment	Yes	62(76(5)	1(1.5)	66(100.0)	147.0	<0.001*
	No	19(23.5)	65(98.5)	0(0.0)		
MontrealCognitive Assessment	Yes	53(65.4)	1(1.5)	66(100.0)	134.5	<0.001*
	No	28(34.6)	65(98.5)	0(0.0)		

X^2=chi square value, p= probability value, NDH= newly diagnosed hypertensives, NDHCI=newly diagnosesd hypertensives with cognitive impairment, C=controls

Table 1. shows neuropsychological assessment in the NDH, NDHCI and controls. The NDHCI had the highest proportions of negative responses in all the domains. However, the proportions of NDHCI were least in registration of name {25 (37.9%)} and language expression {28(42.4%)}. Above half of the NDHCI had negative responses in other domains in the ascending order of definition of terms {46(69.7%)}, motor response {50(75.8%)}, attention to calculation {61(82.4%)}, memory recall {58(87.9%)}. orientation to time [61(92.4%)], memory short story {62(93.9%)}, orientation to place 63(95.5%), semantic story {64(97.0)}, stick design assessment {65(98.5%)} and Montreal cognitive assessment 65(98.5%). Significant differences were observed in the associations of all the domains of assessment among the three groups of participants. ($p<0.05$). Noteworthy contrasts were seen in the associations of all the domains of assessment among NDH, NDHCI and control ($p<0.05$). The NDHCI had the highest proportions of negative responses in all the domains.

However, the proportions of NDHCI in the domains of recognition were different. The domains with the lowest proportions were registration of name (37.9%) and language expression (42.4%).

More than half of the NDHCI had negative responses in other domains: definition of terms (69.7%) motor response (75.8%)}, attention to calculation (82.4%), memory recall (87.9%). orientation to

time (92.4%), memory short story (93.9%), orientation to place (95.5%), semantic story (97.0%), stick design assessment (98.5%) and Montreal cognitive assessment (98.5%). Different levels of Neurodegeneration associated with cerebrovascular diseases seen in this study have been linked to damages to the vascular system, especially abnormalities of the arteries and vessels supplying the head region, which lead to progressive decline in thinking abilities.

Table 2: Age, Anthropometry and Blood Pressure in Hypertensive's, Hypertensives with Congnitive Impairment and Control.

Index	NDH (n=81)	NDHCI (n=69)	Control (n=66)	P1	P2	P3	P4
Age (years)	63.88±1.01	62.15±0.97	61.71±0.98	0.249	0.121	0.216	0.763
Anthropometry							
Weight (kg)	69.14±1.09	72.36± 0.88	58.42 ± 0.82	<0.001∗	<0.001∗	<0.001∗	0.018∗
Height (m)	1.57±0.01	1.61±0.01	1.57±0.01	0.001∗	0.934	0.001∗	0.001∗
BMI (kg/m2)	28.30±0.49	28.09±0.36	23.89 ±0.30	<0.001∗	<0.001∗	0.000∗	0.696
WC (cm)	34.74±0.57	37.67±0.61	32.94±0.22	<0.001∗	0.001∗	<0.001∗	<0.001∗
HpC (cm)	39.32±0.24	40.36±0.22	38.79±0.16	<0.001∗	0.080	0.001∗	0.001∗
WHR	0.88±0.01	0.85±0.12	0.83±0.01	<0.001∗	0.031∗	<0.001∗	0.001∗
Blood Pressure							
SBP (mmHg)	167.54±2.83	161.1±2.39	102.12±1.28	<0.001∗	<0.001∗	<0.001∗	0.051
DBP(mmHg)	98.64±1.61	100.76±1.27	77.36±1.10	<0.001∗	<0.001∗	<0.001∗	0.279

n=number of subjects, ∗=significant at p<0.05, P1=values obtained from ANOVA, P2= values compared between hypertensives and controls, P3= values compared between hypertensives with cognitive impairment and controls, P4=values compared hypertensives and hypertensives with cognitive impairment. BMI=Body mass index, WC=Waist circumference, HpC=Hip circumference, WHR= Waist hip ratio, SBP=Systolic blod pressure, DBP=Diastolic blood pressure. NDH= newly diagnosed hypertensives, NDHCI= newly diagnosed hypertensiveswith cognitive impairment. Values are in mean±SD

Table 2: Shows comparison of age, anthropometry and blood pressure in NDH and NDHCI) and control. The ages of all the 3 groups were similar (p>0.05). Weight, WC and WHR measures in NDHCI were higher than NDH, which were higher than control. The SBP, DBP and BMI were higher in NDH and NDHCI than control while, height and HC were higher in NDHCI than NDH and control (p<0.02).

Table 3: Albumin, interleukin-6 and C-reactive protein levels in, hypertensives, hypertensives with cognitive impairment and control.

Inflammatory Markers	NDH(n=81)	NDHCI(n=69)	C (n=66)	P1	P2	P3	P4
HS-CRP (mg/L)	0.12±0.01	0.14±0.00	0.11±0.00	<0.001*	0.149	<0.001*	0.001*
IL-6 (ng/mL)	115.61 ±15.97	301.55 ±17.58	51.41 ± 1.60	<0.001*	0.002*	<0.001*	<0.001*
ALB (g/dL)	4.20 ± 0.40	4.80±0.52	4.90 ± 0.59	<0.001*	0.001*	0.001*	0.919
Cognitive Score 0-30	18.77± 0.50	3.48±0.38	28.67±0.16	<0.001*	0.001*	0.001*	0.001*

N=number of participants,*=significant at p<0.05, P1=values obtained from ANOVA, P2= values compared between hypertensives and controls, P3= values compared between hypertensives with cognitive impairment and controls, P4=values compared hypertensives and hypertensives with cognitive impairment, ALB=Albumin, IL-6=Interleukin 6, Hs-CRP=High sensitivity C-reactive protein, Values are in mean±2SD.

Table 3 shows comparisons of lipids and cognitive score in NDH, NDHCI and control. Plasma TC, TG, LDL-c, in NDHCI was higher than NDH which were higher than control. HDLC was lower in NDH and NDHCI than control (p<0.01).

Table 4: Multiple Regression of Anthropometric, Antioxidants, Inflammatory biomarkers and Cognitive Score in Hypertensives, Hypertensives with Cognitive Impairment and Controls.

Groups	Dependent	Predictors	B	T	P
NDH	SBP	HS-CRP	225.22	3.801	0.001*
		SOD	0.843	0.205	0.043
	DBP	WC	12.315	2.008	0.049
		HpC	12.241	2.143	0.036
		WHR	496.374	2.070	0.043
	Cognitive Score	WHR	-14.627	-2.932	0.004
		Height	13.365	2.325	0.023*
	HpC	HpC	0.493	2.115	0.038*

NDHCI	SBP	WC	1.291	2.778	0.007*
	DBP	GSH	0.406	5002.570	0.013*
Controls	SBP	HS-CRP	118.557	3.261	0.002*
		Catalase	0.024	2.882	0.005*
		GSH	0.347	3.224	0.002*

β=standard coefficient, SBP=systolic blood pressure, DBP=diastolic blood pressure, HS-CRP=High sensitive C-reactive protein, SOD=superoxide dismutase, WC=waist circumference, HpC= hip circumference, WHR=waist hip ratio, GSH= glutathione, NDH= Newly diagnosed Hypertensives, NDHCI=Newly diagonised Hypertensives with cognitive impairment, T=

Table 4: shows the multiple regressions of anthropometric, antioxidants, biomarkers of inflammation and cognitive impairment in NDH, NDHCI and control. In the NDH group, hs-CRP, SOD had a significantly positive relationship with SBP (β=225.22; β=0.843, respectively) while WC, HC and WHR had a significantly positive relationship with DBP (β=12.315; β=12.241; β=496.374, respectively). In the NDHCI, WC had a positive and significant relationship with SBP (β=1.291) while GSH had a significantly positive relationship with DBP (β=0.406; β=0.022, respectively). In control, hs-CRP, catalase and GSH had positive relationship with SBP (β=118.557; β=0.024; β=0.347, respectively). Height and HC had positive while WHR (in NDH) had inverse relationships with cognitive score (R^2=0.139, 0.186, 0.306, 0.119; β =11.863,0.493) respectively.

Moreover, WC, HC and WHR in NDH group, had a significantly positive relationship with DBP. These outcomes may propose the involvement of lipid peroxidation in hypertension.

CONCLUSION

Increase in inflammatory biomarkers with decrease in antioxidants facilitates progression of hypertension to cognitive impairment in Nigerian hypertensive adults.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

Informed consent was obtained from all participating patients.

REFERENCES

Meredith Hay , Carol Barners , Lee Ryan. Hypertension and age related congnitive impairment : Common Risk factors and a Role for precision Aging Current Hypertension report . (2020); 22:80 .

Arvanitaku Z , Shah RC , Bennett D.A. Diagnosis and management of Dementia : Review JAMA . (2019) 322 : 1589-1599.

Sanchez Hoffmann S, Winkler A, Weimar C, Müller-Gerards D, Abramowski J, Moebus S, Jöckel KH, Erbel R, Jokisch M. Blood pressure and cognitive decline–the impact of hypertension over one decade. Aging, Neuropsychology, and Cognition. 2020 Jul 18:1-5.

Jamainia A , Javanmardifard S , Akbari H ,Sadeghi F , Bijani M. Association between cognitive impairment and Blood pressure among patients with Type II Diabetes mellitus in southern Iran . (2020).

Endy Juli Anto , Laura Octavina Siagian , and Sony Eka Nugrahan. The relationship between Hypertension and Cognitive function impairment in the elderly . Open access Vacedonian Journal of medical science . (2019).

Taraghiz , Kainrani AA , Foroughan M , Yazdani J , Madhavi A , Baghernejad SK, et al. Cognitive impairment among elderly patients with chronic heart failure and related factors . Iranian journal of psychiatry and behavioral Sciences : (2016) ;10 (2) .

Rebled GAC, Serrano SJ, Antón LRL, Aznar TC, Aragüés MG. Occupation and Risk of Cognitive Impairment and Dementia in People in over 55 Years: A Systematic Review, Spain. Rev Esp Salud Publica. (2016); 90:e1-e15

YG - Nan Out , Chen - Chen Tan , Xue - Ning Shan , Whei Xu ,Xiao - He Hou , Qiang Dong , et al. Blood pressure and Risk of Cognitive impairment and Dementia : A systematic Review and Meta -

Analysis of 2019 prospective studies. HYPERTENSION AHA.120.1.Hypertension. (2020) ; 76 : 217 - 225 .

Giovanni Candiano,Andrea Petretto, Maurizio Brusch,Laura Santucci, Veronica Dimuccio, Marco Kalaria RN, et al. Stroke injury, cognitive impairment and vascular dementia. Biochim Biophys Acta. (2016); 1862.5:

Seyed Mehrdad, Hamrahian, Vecihi Batuman. FASN Pathophysiology of Hypertension Updated: Cell Metab. 2008 Jun; 7(6): 476–484.

U. Sahab, Abdullah A M, Saddam H,Muhammad A, Ali A. Sarwar H. et al. Neuroprotective Effect of Phyllanthus acidus L. on Learning and Memory Impairment in Scopolamine-Induced Animal Model of Dementia and Oxidative Stress: Natural Wonder for Regulating the Development and Progression of Alzheimer's Disease. Advances in Alzheimer's disease, (2016); 5.

M. Tadic, Cuspidi C and Hering D. Hypertension and cognitive dysfunction in elderly: blood pressure management for this global burden. BMC Cardiovascular Disorders. (2016); 16.

Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016 Aug 9;134(6):441-50.

K. Amelia, Boehme, Charles Esenwa, Mitchell S.V. Elkind. Stroke Risk Factors, Genetics, and Prevention Circulation Research. ; (2017).