

OBESITY AND DYSLIPIDEMIA AS RISK FACTORS OF VASCULAR COGNITIVE IMPAIRMENT IN ADULT HYPERTENSIVE NIGERIAN

Abstract

Hypertension impairs the cerebral vasculature resulting in vascular cognitive impairment (VCI). The role of obesity and plasma lipids shown as risk factors in development of VCI in adults with hypertension is unclear and is investigated in this study.

Methods

Normoglycemic individuals (n=216) aged 40-75 years were enrolled into this study between January and December 2019. They included Newly Diagnosed Hypertensives with (NDHCI, n=69) and without Cognitive Impairment (NDH, n=81), age-matched with 66 apparently healthy individuals (Controls). Anthropometric measures [height, weight, waist circumference (WC), Hip circumference (HC), waist hip ratio (WHR) and body mass index (BMI)] and socio-demographic indices, lifestyle and blood pressure were obtained using standard methods. Plasma lipids [Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), Triglyceride (TG)] were determined spectrophotometrically, while low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula. Neuropsychological assessment based on cognitive score (CS) was done using community screening instrument for dementia (CSID). Data were analyzed using statistical package for social sciences (SPSS) software 17.0 version. Analysis of variance (ANOVA) and Post Hoc test were used for comparison of variables while Chi square test was used to find associations between variables. These were considered significant at $p < 0.05$.

Results

The obesity indicators (WHR, WC and BMI) and dyslipidemia indicators (TC, LDL-C and triglyceride) levels were significantly higher in NDHCI (WHR=76.97±0.89, WC=37.67±0.61, BMI=28.09±0.49; TC=206.89±3.91, LDL-C=135.76±3.81, triglyceride=135.38±1.63) and NDH (WHR=70.71 ± 0.10, WC=34.74 ± 0.04, BMI= 28.30 ± 0.49 and TC=192.83 ± 4.28, LDL-C= 120.35 ±

3.22, Triglyceride=127.00 ± 2.69) relative to control (WHR=51.99 ± 0.83, WC=32.94 ± 0.22, BMI=23.89 ± 0.30 and TC=104.70 ± 7.19, LDL-C= 94.80 ± 1.90, Triglyceride=72.77 ± 3.70), $p < 0.01$. Significantly low cognitive scores were found in NDHCI (3.48±0.38) compared with NDH (18.77±0.50) and control (28.76±0.16), $p < 0.001$. WHR and LDL-C had inverse relationships with cognitive score in NDH ($\beta = -14.627$, $p = 0.306$) and NDHCI ($\beta = -0.031$, $p = 0.005$) respectively. Moreover, WC ($\beta = 12.315$, $p = 0.049$), HC ($\beta = 12.241$, $p = 0.036$) and WHR ($\beta = 496.374$, $p = 0.043$) in NDH group, had a significantly positive relationship with DBP.

Conclusion

Obesity and arterogenic dyslipidaemia may be associated with the progression of hypertension to cognitive impairment in Nigerian hypertensive adults.

Keywords: Obesity, Artherogenic dyslipidemia, Cognitive Impairment, Adult Hypertensive

INTRODUCTION

Dementia, one of the major causes of disability in older people is a complex syndrome characterized by global and irreversible cognitive decline that is severe enough to undermine daily functioning. About a decade ago, the American Psychiatric Association reported that 57.7% of people living with dementia lived in developing countries; a proportionate increase to 70.5% by 2050 is anticipated (1). Dementia can result from impairment of cognition, which is one of the foremost health complications in normal aged life if left uncontrolled (2)

Vascular cognitive impairment (VCI) is a board spectrum of cognitive and behavioral changes associated with cerebral vascular pathology, characterized by impairment of attention and executive function (including planning, task flexibility, problem solving) ranging from early cognitive decline to dementia. It is a chronic illness that arises from the interplay of genetic, environment and behavioral factors that severely affect social / physical activities and quality of life (2, 3). Goldstein reported an association of hypertension with a wide variety of cognitive deficits including reduced abstract reasoning, executive dysfunction, impaired memory, attention deficits and slowing of mental processing speed (4).

Hypertension (HTN) is a public health problem in both developed and developing countries, with increasing importance as the major cause of cardiovascular diseases; the leading cause of death worldwide (5). It is estimated to affect about 1.56 billion people globally by 2025 (6). An estimate of 60 to 70% of HTN in adults is attributable to adiposity. Abdominal obesity, elevated waist circumference and increased body mass index ($BMI \geq 30 \text{ kg/m}^2$) are independent risk factors for the development and progression of hypertension (7).

Hypertension is the leading risk factor for intracranial and extracranial atherosclerosis. Extracranial lesion is characterized by lipid accumulation in carotid and vertebral arteries, often associated with ulceration and atheroma. This is caused by accumulated fatty deposit and scar tissues which leads to restriction of the circulation and a risk of thrombosis, instability and protrusion which are linked to artery-to-artery embolism. Intracranial lesions affect the circle of willis and its major branches which could result in vascular occlusion and final ischemic stroke (8)

Hypertension in Nigeria affects over 70% of the population (9, 10). It is therefore necessary to prevent the onset of dementia via vascular cognitive impairment by identifying important risk factors for the progression of hypertension. This study is aimed at evaluating obesity and dyslipidemia as probable independent risk factors for the progression of hypertension to vascular cognitive impairment.

MATERIALS AND METHOD

Study Design

This study is a case control. Participants were enrolled at Medical Outpatient Unit of the University College Hospital between January and December, 2019 on their Clinic days.

Study Area

The study area was the University College Hospital Ibadan and its environs.

MATERIALS AND METHODS

Study Population

Two hundred and sixteen participants, aged 40-75 years were enrolled into this study. They consisted of newly diagnosed hypertensives without cognitive impairment, NDH (n=81), newly diagnosed hypertensives with cognitive impairment, NDHCI (n=69) and non hypertensives, non-diabetics with intact cognition, Controls (n=66).

Participants with Hypertension

Newly diagnosed hypertensives with systolic blood pressure (SBP) of ≥ 140 and diastolic blood pressure (DBP) of ≥ 90 mmHg were enrolled into this study. They were non-diabetic, without stroke, without lipid lowering drugs or antihypertensive drugs and had no family history of vascular cognitive impairment. The diagnosis of hypertension was based on the guidelines of the Joint National Committee on hypertension (JNC 7, 2012). Stage 1 hypertension was SBP =140 – 159 mmHg and DBP 90-99 mmHg while Stage 2 hypertension was SBP: ≥ 160 mmHg and DBP ≥ 100 mmHg. Diagnosis was made by a consultant Nephrologists at the Medical outpatients Department of the University College Hospital Ibadan.

Participants With Hypertension and Cognitive Impairment

Newly diagnosed hypertensives with cognitive impairment participants whose SBP were ≥ 140 and DBP of ≥ 90 mmHg and cognitive score were between 0 and 20 (normal reference Range being 0-30 score) were enrolled into this study. They were non-diabetic, without stroke, without lipid lowering drugs or antihypertensive drugs, and had no family history of vascular cognitive impairment. Diagnosis of hypertension with cognitive impairment was based on the guidelines of JNC 7 and CSI-D. The CSI-D was validated by the systematic mini mental state examination (SMMSE) (2). Diagnosis was made by a Consultant Neurologist at the Medical Outpatient Department of the University College Hospital Ibadan.

Controls

These were apparently healthy, normotensive and non-diabetics participants with intact cognitive function as certified by the Neurologist. They were neither on lipid lowering nor antihypertensive medications.

Demographic and Anthropometric Characteristics

Demographic Indices: Semi structured questionnaire was completed by each participant in order to obtain demographic data; 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 lifestyle.

Anthropometric Indices: The anthropometric indices measured were; height, weight, body mass index(BMI), waist circumference(WC), hip circumference(HC) and waist hip ratio(WHR), using standard methods.

Body Weight

These were taken using a balance beam scale. The participants dressed in light clothing, stood bare footed on the scale placed on a flat surface. The weight was moved until the beam balances (the arrow aligned) and the weight was recorded to the nearest 0.1kg

Height

The height of each participant was measured in meters. The participants stood bare footed as upright as possible on a hard level ground against a vertical wall without raising their heels from the ground. Their feet were kept together while the back and heel were aligned with a ruled bar against the vertical surface. Measurement was made by moving a sliding headpiece to the vertex of the participants head and the reading at that point was recorded to the nearest 0.1m.

Body Mass Index (BMI)

This was calculated from the body weight and height by dividing the body weight by the height square as indicated below:

$$\text{BMI} = \text{Body weight (kg)} / \text{Height square (m}^2\text{)}.$$

Waist circumference (WC)

The waist circumference (cm) of each participants was measured using a measuring tape placed at the umbilical level. The subjects stood upright, undressed from waist up to the chest and the waist circumference was measured from the tip of the iliac Crest up the boarder of the 12th rib using standard tape. The measurements were recorded accordingly to the nearest 0.1cm.

Hip Circumference (HC)

The hip circumference of each subject was measured in centimetres (cm). The subjects stood as upright as possible and the hip circumference was measured as the widest circumference of the hip over light clothing using a non- stretchable tape measure, without any pressure to the body surface and was recorded to the nearest 0.1cm.

Waist Hip Ratio (WHR)

This was calculated by dividing the waist circumference by the hip circumference

WHR= Waist circumference (cm) / Hip circumference (cm).

Blood Pressure

BP measurements were performed using a mercury sphygmomanometer. Adequately sized cuffs (standard cuff of 23×12cm) according to arm circumference were placed on the non-dominant arm. The first and the fifth Korotkoff sounds were taken as the systolic and diastolic blood pressure respectfully. The measurements were taken after the patient had rested for 10minutes in the sitting position, rested their back, legs resting on the ground (not crossed), empty bladder, with arm comfortably placed at the heart level. Two measurements were taken at 2minutes intervals. The mean of the set of two measurements was calculated to give SBP and DBP respectively. Clinical hypertension was defined as a $BP \geq 140/90$ mmHg (AHA,,2019)

Measurements of Cognitive Function

The Community screening instrument for dementia (CSID) was used to assess cognitive function and results in a score of 30 (normal) 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 SMMSE a reliable instrument that allows practitioners to accurately measure cognitive deficits and deterioration over time (11).

Sample Collection

Venous blood (10mL) was collected aseptically from the participants after an overnight fasting by venipuncture. This was done by applying tourniquet 4-6inches (10-15cm) above the intended puncture site to obstruct the return of blood to the heart and to distend the vein. The site of the puncture, the media cubital vein in the antecubital fossa was first cleansed with alcohol, the blood was collected with new disposable pyrogen free needles and syringe after the skin had dried.

Blood (2mL) was dispensed into fluoride oxalate bottle, this was used to analyse fasting plasma glucose immediately after sample collection (Randox Laboratory Ltd, Ireland). The remaining blood (3mL) was dispensed into ethylene diamine tetra acetic acid (EDTA) bottle for the analysis of lipids (total cholesterol, high density lipoprotein and triglyceride)(Randox Laboratory Ltd, Ireland) while LDL-C was calculated using frieldewald's formulae. All bottles were labeled appropriately and centrifuged at 500g for five minutes after which plasma was extracted and stored in the fridge in small aliquots at -20°C until analysis.

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). Data analysed were considered significant at $p < 0.05$.

For quantitative variables: Analysis of variance was used to test significance of variations and Post Hoc test 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.

Table 1: Age, Anthropometry and Blood Pressure in Hypertensives, Hypertensives with Cognitive Impairment and Apparently Healthy Normotensive Individuals with Intact Cognition.

Index	Control (n=66)	NDH (n=81)	NDHCI (n=69)	P1	P2	P3	P4
Age (years)	61.71±0.98	63.88±1.01	62.15±0.97	0.249	0.121	0.216	0.763
Anthropometry							
Weight (kg)	58.42 ± 0.82	69.14±1.09	72.36± 0.88	<0.001*	<0.001*	<0.001*	0.018*
Height (m)	1.57±0.01	1.57±0.01	1.61±0.01	0.001*	0.934	0.001*	0.001*
BMI (kg/m ²)	23.89 ±0.30	28.30±0.49	28.09±0.36	<0.001*	<0.001*	0.000*	0.696
WC (cm)	32.94±0.22	34.74±0.57	37.67±0.61	<0.001*	0.001*	<0.001*	<0.001*
HC (cm)	38.79±0.16	39.32±0.24	40.36±0.22	<0.001*	0.080	0.001*	0.001*
WHR	51.99±0.83	70.71±0.10	76.97±0.89	<0.001*	0.031*	<0.001*	0.001*

Blood Pressure

SBP (mmHg)	102.12±1.28	167.54±2.83	161.1±2.39	<0.001*	<0.001*	<0.001*	0.051
DBP(mmHg)	77.36±1.10	98.64±1.61	100.76±1.27	<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, HC=Hip circumference, WHR= Waist hip ratio, SBP=Systolic blood pressure, DBP=Diastolic blood pressure. NDH=newly diagnosed hypertensives, NDHCI= newly diagnosed hypertensives with cognitive impairment. Values are in mean±SD.

Table 2: Lipids and Cognitive Score in Hypertensives, Hypertensives with Cognitive Impairment and Apparently Healthy Normotensive Individuals with Intact Cognition.

Index	Control (n=66)	NDH (n=81)	NDHCI (n=69)	P1	P2	P3	P4
Lipids							
TC(mg/dL)	104.70±7.19	192.83±4.28	206.89±3.91	0.001*	0.001*	<0.001*	0.055
TG (mg/dL)	72.77±3.70	127.00±2.69	135.38±1.69	0.001*	0.001*	0.001*	0.007*
HDL(mg/dL)	52.29±2.97	44.65±0.29	40.30±2.97	0.001*	0.001*	0.001*	0.877
LDL(mg/dL)	94.80±1.90	120.35±3.22	135.76±3.81	0.001*	0.001*	0.001*	0.001*

Cognitive**Score**

0-30 28.67±0.16 18.77± 0.50 3.48±0.38 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, TC=Total cholesterol, TG=Triglyceride, HDL=High density lipoprotein, LDL=Low density, Values are in mean ± SD.

Table 3: Multiple Regression of Anthropometric, Lipids and Cognitive Score in Hypertensives, Hypertensives with Cognitive Impairment and Apparently Healthy Normotensive Individuals with Intact Cognition.

Groups	Dependent	Predictors	B	T	P
NDH	DBP	WC	12.315	2.008	0.049*

		HC	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*
	HC	HC	0.493	2.115	0.038*
NDHCI	SBP	WC	1.291	2.778	0.007*
	Cognitive Score	LDL	-0.031	2.934	0.005*
CONTROL	Height	WHR	0.044	2.143	0.054

β =standard coefficient, SBP=systolic blood pressure, DBP=diastolic blood pressure, WC=waist circumference, HpC= hip circumference, WHR=waist hip ratio, , TG=triglyceride, LDL= low density lipoprotein, NDH=Newly diagnosed Hypertensives, NDHCI=Newly diagnosed Hypertensives with cognitive impairment,

Table 1 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 progressed in NDH to NDHCI relative to control. The SBP, DBP and BMI were higher in NDH and NDHCI than control while, height and HC were higher in NDHCI relative to NDH and control ($p<0.02$). Table 2 shows comparisons of lipids and cognitive score in NDH, NDHCI and control. Plasma TC, TG, LDL-C progressed from NDH to NDHCI relative to control. HDL-C was lower in NDH and NDHCI than control ($p<0.01$).

Table 3 shows the relationship of Anthropometrics, Lipids and Cognitive score in NDH, NDHCl and control. WC, HC and WHR in NDH, had a significantly positive relationship with DBP ($\beta=12.315$, $p=0.049$; $\beta=12.241$, $p=0.036$; $\beta=496.374$, $p=0.043$), respectively. LDL-C had inverse relationships with cognitive score in NDH ($\beta= -14.627$, $p= 0.306$) and NDHCl ($\beta= -0.031$, $p=0.005$) respectively. There is progressive increase in the anthropometrics and lipids from control to NDH and NDHCl with a significant and corresponding decrease in the cognitive scores. This outcome may propose the involvement of lipid peroxidation in hypertension and the possibility of direct association of LDL-C in the progression of hypertension to cognitive impairment.

DISCUSSION

Hypertension is a modifiable risk factor that is associated with cognitive impairment, which has been attributed to underlying pathologies of dyslipidaemia. Thus, prevention of hypertension has been reported to delay cognitive loss (12). In this present study, the ages of the NDH, NDHCl and control were similar ($p>0.05$), so the findings may not be attributed to age.

Dyslipidaemia in Hypertension and Cognitive Impairment

Hypertension advances development of atherosclerotic plaques in cerebral supply routes and arterioles, which may prompt blood vessel occlusion. Results with respect to relationship between dyslipidaemia and cognitive impairment are conflicting (13). However, in this research, there were progressive increases in total cholesterol, triglyceride, and low density lipoprotein cholesterol (LDL-c) from control to NDH to NDHCl with corresponding decrease in cognitive score. Only LDL cholesterol had an inverse relationship with cognitive score. Dyslipidaemia in hypertensives with and without cognitive impairment has been reported previously (13). Increasing levels of these lipids particularly LDL-c may be associated with the progression from hypertension to cognitive impairment and may be early biomarkers of cognitive impairment in hypertensives. In cross sectional studies of men with vascular cognitive impairment disease,

plasma triglyceride as well as LDL-c levels were increased. Plasma triglyceride had previously been shown as a free risk factor for the development of VCI (14). High level of Low density lipoprotein-cholesterol has been observed to be related to hippocampal volume and dementia (15,16). Low HDL-c level is a risk factor for atherosclerosis and stroke and has been embroiled in dementia (17). In this investigation, reduced level of HDL-C level was observed in NDH and NDHCI compared with control ($p<0.01$).

Anthropometry, Hypertension and Cognitive Impairment

Abdominal obesity indicators (WC, WHR, and BMI) increased progressively from control to NDH and NDHCI in this study, linking altered anthropometrics with cognitive impairment. These indicators of obesity may be early markers of cognitive impairment (18, 19). Moreover, WHR had an indirect relationship with cognitive score in hypertensives ($p<0.004$). Increased HC (an indicator of subcutaneous obesity) was higher in NDHCI than NDH and control. The direct relationship of elevated HC with obesity may be linked with cognitive decline in hypertensives. Body mass index was associated with hypertension and not cognitive impairment in this study, as it was higher in NDH than NDHCI and control ($p<0.02$). Whitmer (2008) and Shenc, (2019), reported that abdominal obesity could be more dangerous risk factor for dementia, cardiovascular disease and diabetes than total body obesity. Central obesity in midlife increased the risk of dementia independent of diabetes and cardiovascular comorbidities in their study (19).

Hypertension and Cognitive Impairment

The SBP and DBP were higher in NDH and NDHCI than control, 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 in all groups. Cognitive impairment may be present irrespective of blood pressure readings in hypertensives contrary to reports by McDonald *et al.* (2017).

RECOMMENDATION

1. Regular assessment of HC, weight, WC and WHR (altered anthropometry), TC, TG, LDLC (dyslipidaemia), may be needed to prevent progression from hypertension to cognitive impairment.
2. Improved lifestyle including dietary modification and physical activity aimed at weight reduction are recommended.

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