ORIGINAL ARTICLE

Elevated lipoprotein (a) levels in hypertensive patients in southern part of Nigeria

Augustine Onovuakpo Eguvbe[1], Thompson Onoriedeode Ologbo[2], Ufuoma Blessing Ofili[1], Ekata Agnes Oghenekaro[3]

[1]Department of Chemical Pathology, Delta State University, Abraka, Delta State, Nigeria.
[2]Department of Haematology and Blood Transfusion, Delta State University, Abraka, Delta State, Nigeria.
[3]Department of Chemical Pathology, Delta State University Teaching Hospital, Oghara, Delta State, Nigeria

Corresponding Author: Augustine Onovuakpo Eguvbe **Email:** augustine.eguvbe@delsu.edu.ng

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ABSTRACT

Hypertension is linked to an increased risk of cardiovascular disease and is the leading modifiable risk factor for morbidity and mortality globally. Lipoprotein (a) is an independent risk factor for atherosclerotic cardiovascular disease. It has been suggested that Lp (a) contributes to an increased risk for atherosclerosis in hypertensive patients. This study was to investigate the levels of Lp (a) in hypertensive patients and correlate them with other risk factors of cardiovascular disease. This was a hospital-based cross-sectional study conducted between October 2022 and December 2023 at the Delta State Central Hospital, Warri. Three hundred participants consisting of two hundred hypertensive and one hundred normotensive individuals were recruited for the study. The study used a structured interviewer-administered questionnaire to collect data, which was then analyzed using SPSS version 23. One hundred and fifteen (57.5%) hypertensives and fifteen (15%) normotensive controls had plasma concentrations of Lp (a) above 30 mg/dl. The Lp (a) levels in the hypertensives ranged from 5.2 – 89.0 mg/dl with a mean of 32.8 ± 16.6 mg/dl. The controls had a range of 1.1 – 63.2 mg/dl with a mean of 16.9 ± 13.9 mg/dl. The difference in mean Lp (a) levels was statistically significant ($p < 0.001$). In the hypertensives, Lp (a) correlated positively with body weight ($r = 0.522$, $p = 0.001$), BMI ($r = 0.553$, $p = 0.002$) and waist circumference ($r = 0.628$, $p = 0.001$). In the hypertensive population, obesity was a stronger predictor of Lp (a) levels than the female gender (OR: 3.6, 95% CI: 1.4 – 9.8, $p = 0.010$) and (OR 9.3; 95% CI: 2.5 – 34.0, $p = 0.001$). Lp (a) levels were significantly higher in the hypertensive patients than in the normotensive controls. There was a positive correlation between Lp (a) and BMI and waist circumference in the hypertensive group. Obesity had a higher predictive value for the Lp (a) levels than the female gender. Periodic screening for serum Lp (a) in hypertensive patients could be very useful in assessing the risk of cardiovascular disease.

Key words:
hypertension; lipoprotein (a); body mass index; waist circumference; estimated glomerular filtration rate.

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INTRODUCTION

Hypertension is one of the main causes of death worldwide and is responsible for up to 30% of myocardial infarction.[1] It is linked with an increased risk of cardiovascular disease and is the leading modifiable risk factor for morbidity and mortality globally.[2]

Lipoprotein (a), (Lp[a]), a spherical macromolecular complex with an approximate diameter of 25 nm and a density range of 1.05 to 1.12 g/ml, was first identified by Berg in 1963.[3] It is an LDL-like substance, and its structure is apolipoprotein (a) linked by a disulfide bond to apolipoprotein B-100 on the LDL core.[4] It is an independent risk factor for atherosclerotic cardiovascular disease.[5] It has been suggested that Lp (a) contributes to an increased risk for atherosclerosis in hypertensive patients.[4] It enhances the formation of foam cells and deposition of cholesterol in atherosclerotic plaques by binding to macrophages.[6]

In hypertensive patients, high concentration of Lp (a) are an indication of the presence and severity of hypertensive vascular damage.[7] Lp (a) increases the risk of cardiovascular disease via proatherogenic effects of its LDL-like portion, proinflammatory effects of its phospholipid content, and prothrombotic effects via its inactive plasminogen-like protease domain on apolipoprotein (a). Genetically determined low concentrations of Lp (a) (< 30 mg/dl) are linked with a reduced risk of cardiovascular disease.[8]

Lp (a) is produced in the liver. Concentrations of Lp (a) above 20-30 mg/dl are associated with a two-fold increased risk of developing coronary artery disease.[3] The interpretation of Lp (a) result is as follows: Lp (a) < 14 mg/dl is desirable; 14-30 mg/dl is borderline cardiovascular risk; 31-50 mg/dl is high risk range for cardiovascular disease; > 50 mg/dl is very high cardiovascular risk.[9]

In Southern part of Nigeria, hypertension and obesity are prevalent and studies have shown the deficiency of LDL-cholesterol in predicting adverse cardiovascular events.[10, 11] Some studies have reported that increased levels of Lp (a) are associated with an elevated risk of cardiovascular events even in patients with low LDL-cholesterol level.[12, 13] Similar studies on Lp (a) in hypertensive patients have not been done in this environment. Thus, this study will help to identify the need for routine screening for Lp (a) in hypertensive patients. Routine screening will identify more patients at risk for atherosclerotic cardiovascular disease.

Screening hypertensive patients for high concentration of Lp (a) could help to identify those who require more aggressive therapy aimed at reducing lipid levels and modifying other risk factors of cardiovascular disease. Thus, this study was to investigate the levels of Lp (a) in hypertensive patients and correlate them with other risk factors of cardiovascular disease.

METHODS

Study design and population

This was a hospital-based cross-sectional study conducted between October 2022 and December 2023 at the Delta State Central Hospital, Warri. Three hundred participants consisting of two hundred hypertensive and one hundred normotensive individuals were recruited for the study. The hypertensive and normotensive cases were recruited from the General Outpatient Department and the Cardiology Unit of the Delta State Central Hospital, Warri. The inclusion criteria included participants aged eighteen years and above, diagnosed with hypertension (blood pressure ≥ 140/90 mmHg) and normotensive individuals with blood pressure below 140/90 mmHg at the General Outpatient Department and the Cardiology Unit of the Delta State Central

Hospital, Warri. Participants with a history of diabetes mellitus, chronic alcoholism or smoking, renal disease, liver disease, pregnancy, hypothyroidism/hyperthyroidism, hypertriglyceridemia (> 400 mg/dl), hereditary familial hypercholesterolemia/ dyslipoproteinemia, and women on hormone replacement therapy were excluded from the study. Patients on phenytoin, carbamazepine, metformin, pentoxyphylline, methotrexate, vitamin D supplements and lipid-lowering agents were also excluded. Central Hospital Warri is a secondary health facility with 254 beds. They render general and specialized medical and surgical services.

Sample size and sampling procedure

The sample size was calculated from the formula for a cross-sectional study: $n = (Z^2Pq)/d^2$, where n = sample size, Z = standard deviation, P = prevalence of hypertension, q = 1-P and d = degree of precision to be used (0.05). Consecutive sampling was utilized to recruit participants. Three hundred participants consisting of two hundred hypertensive and one hundred normotensive individuals were recruited into the study. Written informed consent was obtained from each study participant. The study used a structured interviewer-administered questionnaire, which included identification number, age, gender, weight, height, waist circumference, medical history and laboratory results. Body mass index (BMI) was calculated from the weight (kg) divided by the height (meter) squared. Waist circumference (WC) was measured with a measuring tape at the approximate midpoint between the lower margin of the palpable rib and the top of the iliac crest.

Data collection

Demographic and baseline characteristics

The study used a structured interviewer-administered questionnaire, which included identification number, age, gender, weight, height, waist circumference, alcohol intake and smoking history, medical history and laboratory results. A detailed history was taken, including past or current co-morbidities. BP was measured using a mercury sphygmomanometer after the patient had rested for at least ten minutes. The reading at the first appearance of the Korotkoff sound (phase I) was taken as the systolic BP and that at its disappearance (phase V) was taken as the diastolic blood pressure. Hypertension was defined as values 140/90 mmHg and above on two or more different occasions.[14] Height was measured by a stadiometer. Weight was measured using an electronic patient weighing scale. Body mass index (BMI) was calculated by dividing weight (kg) by the height (meter) squared. Obesity was defined as a BMI equal to or greater than 30 kg/m^2. Waist circumference (WC) was measured with a measuring tape at the approximate midpoint between the lower margin of the palpable rib and the top of the iliac crest.

Blood sample

Five milliliters (5 ml) of venous blood was collected from the brachial vein of each participant into a plain bottle and allowed to clot. The samples were separated and the serum was kept at -20°C and analysed weekly. Morning and evening temperature recordings were taken to monitor the temperature of the freezer. Serum level of Lp (a) was analysed by immunoturbidimetry according to the manufacturer's protocol, while serum creatinine was assayed on a spectrophotometer using the kinetic modification of the Jaffe procedure. Estimated glomerular filtration rate (eGFR) was predicted from serum creatinine using the Modification of Diet for Renal Disease formula based on age, sex, race and serum creatinine.[15]

Data analysis

Data was analyzed with SPSS version 23. Continuous variables including age, blood pressure measurements and anthropometric variables, and biochemical parameters were tested for normality. Normally distributed continuous variables were summarized as mean, standard deviation, and ranges. Categorical variables were summarized using frequencies and percentages.

The differences in means of continuous variables between the hypertensive group and controls were compared using the Student's T-test. Chi square test was used for univariate analysis. The Pearson's correlation coefficient was used to correlate Lp (a) with age, blood pressure measurements, anthropometric variables, serum creatinine and eGFR. Multivariate logistic regression analysis was done to determine predictors of lipoprotein (a) levels in hypertensives. Statistical significance was set at <0.05.

Ethical Consent

This study was approved by the ethics and research committee (protocol number: CHW/ECC VOL 1/275) of the Delta State Central Hospital, Warri. Written informed consent was obtained from each study participant and strict confidentiality was observed for participant's data.

RESULTS

A total of 300 participants were recruited for the study including 200 hypertensives and 100 controls. The hypertensives had an age range of 19.0 – 92.0 years with a mean age and standard deviation of 58.2 ± 13.1 years, and the controls had an age range of 22.0 – 66.0 years with a mean age and standard deviation of 43.8 ± 10.7 years. The hypertensives were significantly older than the controls (p = 0.001). The hypertensives included 147 (73.5%)) females and 53 (26.5%) males, while the controls included 53 (53.0%) females and 47 (47.0%) males. The difference in the sex distribution was also statistically significant (p = 0.007) (Table 1).

Anthropometrics

The body weight of the hypertensives and the controls did not differ significantly as shown in Table 1 (χ^2 = 0.675, p = 0.635). The height also did not differ significantly between the hypertensives and controls (1.62 ± 0.07 vs. 1.64 ± 0.09, respectively, p = 0.208). Likewise, the BMI did not differ significantly between them (28.9 ± 6.5 vs. 28.8 ± 5.1 kg/m^2, p = 0.891) (Table 2). Seventy-two (36.0%) of the hypertensives and 35 (35.0%) of the controls were obese (BMI ≥30kg/m^2), as shown in table 1. The difference in proportion was not statistically significant (p = 0.635) (Table 1).

Social history

Only two study participants reported smoking and the subjects were in the control group. There was no significant difference in the distribution of smoking in the study groups (p = 0.723). Thirty-three (16.5%) of the hypertensives reported drinking alcohol compared to 7 (7.0%) of the controls, and the difference in proportion was not statistically (p = 0.067) (Table 1).

Renal function

Serum creatinine was higher in the hypertensives than in the controls, but the difference in mean did not reach statistical significance (1.2 ± 1.1 vs. 1.0 ± 0.2 mg/dl, p = 0.073). The mean eGFR was significantly higher in the hypertensive population than in the controls (80.6 ± 36.9 vs. 91.8 ± 24.2ml/m^2/min, p = 0.035). Seventy-two (36.0%) of the hypertensive subjects had renal impairment (eGFR < 60ml/m^2/min) compared to 32 (32.0%) of the controls. The difference in proportion was not statistically significant p = 0.579).

Lipoprotein (a)

Only one hundred and fifteen (57.5%) hypertensives and fifteen (15%) normotensive controls had plasma concentrations of Lp (a) above 30 mg/dl. The Lp (a) levels in the hypertensives ranged from 5.2 – 89.0 mg/dl with a mean of 32.8 ± 16.6 mg/dl. The controls had a range of 1.1 – 63.2 mg/dl with a mean of 16.9 ± 13.9 mg/dl. The difference in mean Lp (a) levels was statistically significant (p <0.001) (Table 2) (Figure 1).

Table 1: Sociodemographic characteristics of the participants

	Hypertensives n = 200(%)	**Controls n = 100(%)**	**Statistical test**	**P-value**
Age group				
<40	8 (4.0)	30 (30.0)		
40 – 59	97 (48.5)	63 (63.0)	*χ^2 = 38.830	<0.001
≥60	95 (47.5)	7 (7.0)		
Sex				
Male	53 (26.5)	47 (47.0)	χ^2 = 7.200	0.007
Female	147 (73.5)	53 (53.0)		
BMI				
Underweight	3 (1.5)	2 (2.0)		
Normal	55 (27.5)	20 (20.0)	χ^2 = 0.675*	0.635
Overweight	70 (35.0)	43 (43.0)		
Obese	72 (36.0)	35 (35.0)		
Alcohol intake	33 (16.5)	7 (7.0)	Fishers Exact	0.067
Smoking	0 (0.0)	2 (2.0)	Fishers Exact	0.333

*Adjusted Chi square test. BMI: body mass index.

Table 2: Age, blood pressure measurements, anthropometrics and biochemical parameters of the study groups.

	Hypertensives n= 200	**Controls n = 100**	**t value**	**P-value**
Age	58.2 ± 13.0 19.0 – 92.0	43.8 ± 10.7 22.0 – 66.0	7.410	<0.001
SBP	169.2 ± 15.6 140.0 – 220.0	118.3 ± 11.9 60.0 – 90.0	22.252	<0.001
DBP	106.5 ± 9.7 90.0 – 140.0	76.6 ± 7.4 60.0 – 90.0	20.948	<0.001
Weight	76.0 ± 18.0 44.0 – 135.0	76.2 ± 9.2 59.0 – 106.0	-0.067	0.946
Height	1.62 ± 0.07 1.50 – 1.80	1.64 ± 0.09 1.45 – 1.80	-1.265	0.208
BMI	28.9 ± 6.5 16.2 – 51.4	28.8 ± 5.1 18.4 – 41.4	0.137	0.891
Waist circumference	98.8 ± 13.2 70.0 – 149.0	91.3 ± 8.1 80.0 – 129.0	4.056	<0.001
Serum creatinine	1.2 ± 1.1 0.4 – 9.4	1.0 ± 0.2 0.3 – 1.3	1.802	0.073

	Hypertensives n= 200	Controls n = 100	t value	P-value
eGFR	80.6 ± 36.9 5.0 – 277.0	91.8 ± 24.2 55.0 – 171.0	-2.126	0.035
Lp (a)	32.8 ± 16.6 5.2 – 89.0	16.9 ± 13.9 1.1 – 63.2	6.380	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; eGFR:estimated glomerular filtration rate.

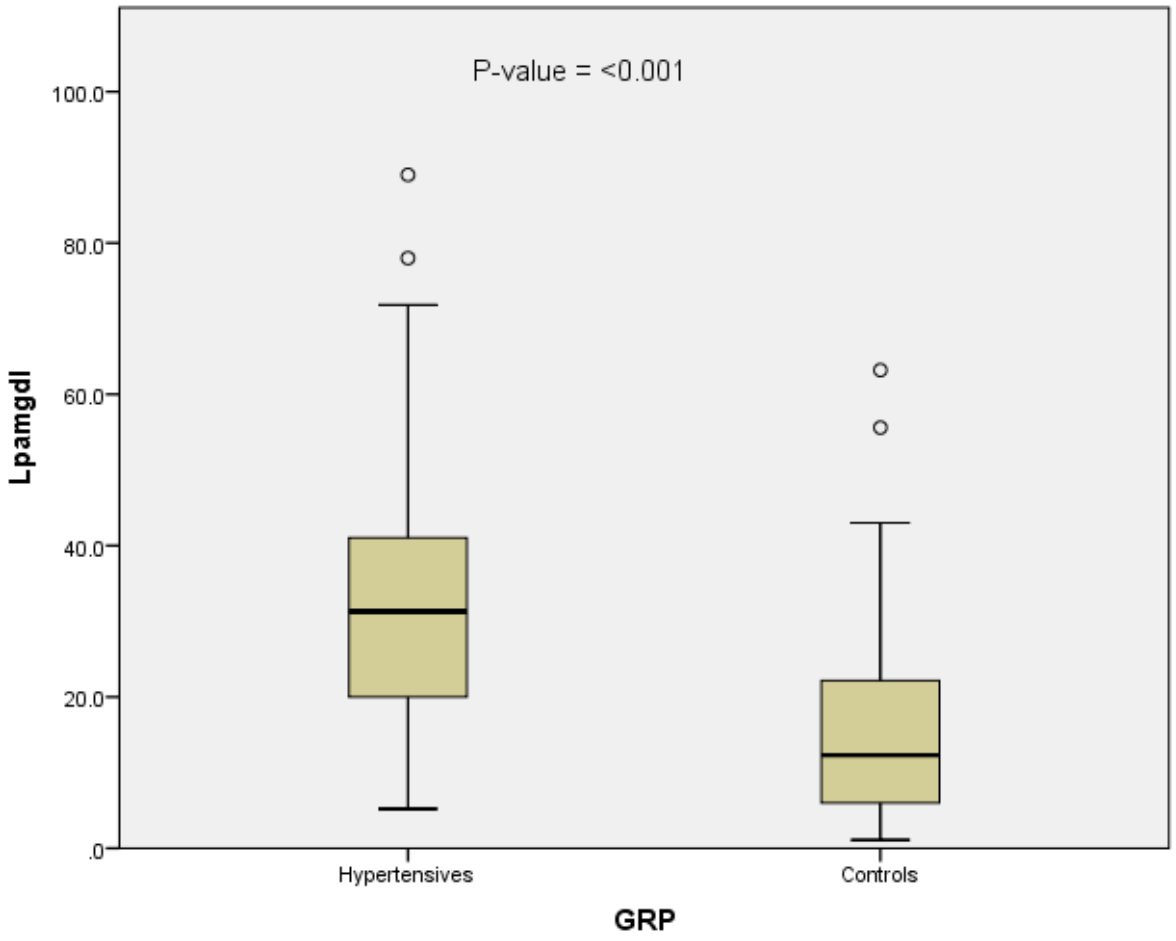

Figure 1. Boxplot showing the distribution of lipoprotein (a) in the study population

Table 3. Correlation of Lp(a) levels with age, blood pressure measurements anthropometric variables, creatinine and eGFR in hypertensives and controls.

Hypertensives	**r**	**P-value**
Age	0.139	0.131
SBP	-0.150	0.101
DBP	-0.038	0.678
BMI	0.553	0.002
WC	0.628	0.001
Serum Cr	-0.065	0.479
eGFR	-0.036	0.697
Controls	**r**	**P-value**
Age	0.012	0.929
SBP	-0.012	0.925
DBP	-0.061	0.645
BMI	-0.088	0.502
WC	0.122	0.354
Serum Cr	0.120	0.363
eGFR	-0.198	0.129

Dependent variable: Lp (a). SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; eGFR: estimated glomerular filtration rate; WC: waist circumference; Cr: creatinine

In the hypertensives, Lp(a) correlated positively with body weight (r = 0.522, p = 0.001), BMI (r = 0.553, p = 0.002) and waist circumference (r = 0.628, p = 0.001) (Table 3).

In the controls, there were no significant correlations between Lp (a), age, blood pressure indices, anthropometric variables and renal parameters (serum creatinine and eGFR).

Table 4. Multivariate regression analysis on Lipoprotein (a) with age, sex, BMI and eGFR

Hypertensives		**B**	**OR**	**95% CI**	**P-value**
Age	≥60yrs <60yrs[ref]	0.457	1.6	0.6 – 3.9	0.323
Sex	F M [ref]	1.297	3.6	1.4 – 9.8	0.010
BMI	Obesity Normal[ref]	2.228	9.3	2.5 – 34.0	0.001
eGFR	≥60 <60 [ref]	0.514	1.7	0.6 – 4.7	0.331
Controls		**B**	**OR**	**95% CI**	**P-value**
Age	≥60yrs <60yrs [ref]	2.109	8.2	0.8 – 89.5	0.083
Sex	F M [ref]	0.548	1.7	0.5 – 6.0	0.387
BMI	Obesity Normal [ref]	0.156	1.2	0.3 – 4.1	0.810
eGFR	≥60 <60[ref]	-0.089	0.9	0.1 – 8.1	0.936

Dependent variable: Lp(a). BMI: body mass index; eGFR: estimated glomerular filtration rate
Ref. = Reference group

In the hypertensive population, obesity had a higher predictive value than the female gender for Lp(a) levels (OR: 3.6, 95% CI: 1.4 – 9.8, p = 0.010) and (OR 9.3; 95% CI: 2.5 – 34.0, p = 0.001) (Table 4).

In the controls, there were no significant predictors of Lp(a) levels. Though age 60 and above showed high odds, it was not statistically significant (OR: 8.2, 95% CI: 0.8 – 89.5, p = 0.083).

DISCUSSION

In this present study, we determined the levels of Lp (a) in hypertensive patients and compared them with other cardiovascular risk factors. Serum Lp (a) levels were significantly higher in the hypertensive individuals than in the controls, implying a higher risk of atherosclerotic cardiovascular disease in hypertension. In the hypertensives, Lp (a) was positively correlated with body weight, BMI and waist circumference. Also, obesity had a higher predictive value for Lp (a) levels than the female gender.

Consistent with the findings in this study, several studies have documented elevated serum Lp (a) concentrations in hypertensive individuals. Papadakis et al., reported a significantly higher level of serum Lp (a) in untreated hypertensive individuals compared to normotensive controls.[16] In a cross-sectional study involving 100 newly diagnosed cases of hypertension, serum Lp (a) levels were significantly higher than normotensive controls.[17] Also, serum L(a) was found to be significantly higher in hypertensive patients compared to controls in a study among essential hypertensive patients in a tertiary care hospital.[18] In addition, Bhavani et al., reported higher plasma concentrations of Lp (a) in hypertensive patients in a study conducted among untreated hypertensive patients and normotensive controls.[19]

In addition to the findings of elevated Lp (a) in hypertensive patients, it is also an independent risk factor for cardiovascular disease. Lp (a) has been described as an established risk factor for atherosclerosis, coronary artery disease, stroke, thrombosis and aortic stenosis.[9] Thus, the higher level of Lp (a) in hypertensive patients will compound the risk of cardiovascular disease. Rikhi et al., in a large multicenter study, showed that elevated Lp (a) in patients with essential hypertension was associated with a significant increase in cardiovascular disease.[20]Consequently, upon these findings, the European Atherosclerosis Society (EAS) has recommended routine measurement of Lp (a) among patients with moderate to high risk of atherosclerosis and cardiovascular disease.[21]

The present study also reported that Lp (a) was positively correlated with BMI and waist circumference in hypertensive patients but had no correlation in the control group. We could not find similar studies reporting on the association of Lp (a) with BMI in the adult population. However, few studies in the pediatric population reported varying results on the correlation of Lp (a) with BMI. A study on the prevalence and status of Lp (a) among Lebanese school children reported a significant correlation between Lp (a) and BMI.[22] However, Stuerzebecher et al., reported no correlation between serum Lp (a) concentrations and BMI in a study including 605 healthy children aged between 5 and 17 years.[23]

Obesity was a stronger predictor of Lp (a) levels than the female gender in the present study. We were unable to find a similar report in other studies. However, a cross-sectional study by Posadas-Romero et al., reported that obesity with normoinsulinemia was related to increased Lp (a) concentration in men.[24] In a study aimed at evaluating the predictive value of Lp (a) for mortality and non-fatal myocardial infarction, Lp (a) was found to be an independent determinant for cardiovascular events in type 2 diabetic

female subgroup.[25] Also, higher Lp (a) concentrations in women with type 2 diabetes than in men with type 2 diabetes have been implicated in the higher increase in cardiovascular mortality in women than men.[26]

Furthermore, researchers have shown that Lp (a) and BMI have an additive effect in conferring a high risk of cardiovascular disease. A cross-sectional study to assess the synergistic effect of Lp (a) and BMI in first incident myocardial infarction reported that elevated Lp (a) concentrations induce a high risk for initial acute myocardial infarction when BMI is elevated.[27] In a research study undertaken to determine the association between Lp (a) levels and high BMI, involving 69,988 individuals, highly elevated Lp (a) levels and high BMI were found to cause a higher risk of calcific aortic valve disease.[28]

This study has some limitations. History of cardiovascular disease and other related diseases was not collected. Also, being a hospital-based study, it may not truly represent the general population.

RECOMMENDATIONS

Serum Lp (a) levels were significantly higher in the hypertensive patients than in the normotensive controls, suggesting a higher risk of atherosclerotic cardiovascular disease among those with hypertension. Also, there was a positive correlation between serum Lp (a) and BMI and waist circumference in the hypertensive group. Obesity was a stronger predictor of Lp (a) levels than the female gender. The above findings suggest that periodic screening for serum Lp (a) in hypertensive patients can be very useful in assessing the risk of cardiovascular disease. However, additional studies are needed to gain a deeper understanding of the underlying mechanisms linking Lp (a) with hypertension.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest concerning this article.

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