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Hepatic Lipase Influences Plasma Lipid Profiles and Lipoprotein Ratios in Regional Hospital Patients with Ischemic Stroke

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Authors' contributions

This work received the collaboration of all authors. Author MJO designed the methodology protocol, wrote the first manuscript and contributed to the discussion and corrections. Authors OAA and EOAT carried out the statistical analysis and the final revision of the introduction, methodology and discussion. All authors read, discussed and approved the final manuscript.

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ABSTRACT

Background: Stroke is the second most common cause of death and disability in developed Countries. Ischemic stroke is the most common, with an estimated incidence of approximately 80%. Studies have shown that dyslipidemia, including high levels of plasma or serum total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (ApoB) and low levels of high density lipoprotein-cholesterol (HDL-C) is a risk factor for the progression of atherosclerosis and the development of cardiovascular disease. Attempts are being made to include the use of lipoprotein ratios to optimize the predictive capacity of lipid profile in risk evaluation.

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Objective: The objective of the present study is to evaluate the effect of hepatic lipase activity on lipid profiles and lipoprotein ratios in ischemic stroke patients.
Methodology: Two hundred healthy and ischemic stroke subjects were recruited in the study after obtaining informed written consent. They were divided into six groups considering age classes. Group 1-3 were control subjects (n=100) and 4-6 were ischemic stroke subjects (n=100). Weight, height, hepatic lipase activity and plasma lipid profiles were measured and lipoprotein ratios calculated using Excel software. Statistical analyses were performed using GraphPad prism computer software version 5.00 and SPSS version 22 software programme.
Results: Hepatic lipase activity in the stroke subjects was significantly (P<0.0001) lower than control subjects (P=0.0001, 20.21 ± 0.3706 µmol/h/ml vs 30.50 ± 0.3928 µmol/h/ml). The stroke subjects had significantly (P<0.05) higher SBP, DBP and BMI compared to the control. Abnormal plasma lipid parameters were obtained in the stroke subjects compared to the control subjects. The stroke subjects had significant (P<0.0001) elevated TC, TG, LDL-C, VLDL-C, Non- HDL-C, CRI-I, CRI-II, AC, TG/HDL-C and AIP as well as lower HDL-C and HDL-C/LDL-C. LDL-C/HDL-C ratio (0R=490488439.6, 95% CI=0.078 - 3.102E+18 P=0.000) is the major risk factor for the development of ischemic stroke.
Conclusion: Hepatic lipase activities were lower while higher BP, BMI and dyslipidemia were obtained in the ischemic stroke subjects.

Keywords: BP; BMI; dyslipidemia; ischemic stroke; lipid profiles; lipoprotein ratios and hepatic lipase activities.

1. INTRODUCTION

Cardiovascular diseases (CVD) are the first world's leading causes of death [1]. It is a class of diseases that involve the heart or blood vessels (arteries, capillaries and veins), which refers to any disease that affects the cardiovascular system such as: cardiac disease, vascular diseases of the brain and kidney, and peripheral arterial disease [2]. Stroke is the second-leading cause of mortality worldwide [3]. It is the second most common causes of death and disability in developed countries [4]. It is a multifactorial and polygenic disease caused by the interaction of concomitant diseases, environmental and risk factors like smoking, advanced age, blood pressure and diabetes. Most strokes (~ 80%) are ischemic [5] they result from occlusion of a major cerebral artery by a thrombus or embolism. This results in reduced blood flow and a major decrease in the supply of oxygen, glucose and all other nutrients as well as disrupting the nutrient and waste exchange process required to support brain metabolism. If cerebral arterial blood flow is not restored within a short period, cerebral ischemia will result, with subsequent neuron death within the perfusion territory of the vessels affected. Ischemic stroke is characterized by a complex sequence of events that evolves over hours or even days [6-8]. In addition, about one quarter of patients suffering stroke are found to be demented three months later [9].

Epidemiological studies have shown that dyslipidemia, including high levels of plasma or serum total cholesterol (TC) [10] triglycerides (TG) [11] low density lipoprotein-cholesterol (LDL-C) [12] and apolipoprotein B (ApoB) [13] and low levels of high density lipoprotein-cholesterol (HDL-C) [14] are risk factors for the progression of atherosclerosis and the development of cardiovascular disease. Studies have shown that plasma lipid concentrations are modulated by environmental factors such as demographics [15] exercise [16], diet [17], alcohol consumption [18] cigarette smoking [18-19], obesity [20] hypertension [21] as well as genetic factors.

Systolic and diastolic blood pressures have been shown to correlate with increased cardiovascular mortality and stroke in elderly individuals [22]. In adults, overweight is defined as a body mass index (BMI) that range from 25 to 29.9 kg/m^2 and obesity as BMI ≥30 kg/m^2. Obesity has been shown to be an independent risk factor for cardiovascular mortality and an indirect risk factor because of its effect on hypertension, diabetes, dyslipidemia and cardiovascular disease generally [23-25].

Hepatic lipase (HL) is an enzyme that regulates the metabolism of LDL-Cholesterol, intermediate-density lipoprotein (IDL), and HDL particles [26]. It has been demonstrated that high hepatic lipase activity is associated with low HDL-C level, and hepatic lipase helps in the metabolism of TG-rich

HDL_2-C. [27-28]. HL facilitates the hepatic uptake of lipoproteins, including HDL, by acting as a ligand that mediates the binding and uptake of lipoproteins through proteoglycans receptor pathways, or both [29-30]. The human hepatic lipase gene (*LIPC*) is located on chromosome 15q21, spans >120 kb of DNA and encodes a protein of 449 amino acids [31]. HL activity is determined by gender, visceral obesity, insulin resistance, diet, and genotype.

Lipoprotein ratios have been recently used to predict the risk of cardiovascular diseases. Some of these ratios are: TC/HDL-C (Castelli risk index-I), LDL- C/HDL-C (Castelli risk index-II), TG/HDL-C, Logarithmic transformation of TG/HDL-C (Atherogenic index of plasma i.e AIP), HDL-C/TC (Coronary disease risk ratio), HDL-C/LDL-C and Atherogenic coefficient (AC) = (TC-HDL-C)/HDL-C. Jeppesen et al. [32] shows that the better ability of these lipoprotein ratios to predict cardiovascular disease compared to single lipid marker is of particular clinical relevance and can be possibly explained by association of lipid ratios with a cluster of cardiovascular risk factors that are at least in part unrelated to cholesterol metabolism. The object of the study was to evaluate the influence of hepatic lipase on lipid profiles and lipoprotein ratios in ischemic stroke patients.

2. MATERIALS AND METHODS

2.1 Study Subjects

This pilot study involved 100 adult Ischemic stroke subjects who visited Lagos Universtity Teaching Hospital (LUTH) in South-West, Nigeria were obtained for the analysis. The sample size calculation for the study was based on the formula: $n=Z^2Pq/ d^2$ (Mugwe and Mbaja, 2013 [33] where: n=sample size, Z=1.96 (95% confidence level) P=Prevalence = 6.7% (0.067) (Michiel et al. (34); q= Complementary probability= 1-P =1-0.067=0.933 and d=Sample error (5%) =0.05. All the ischemic stroke patients had cerebral computerized tomography taken which showed cerebral infarction and they were confirmed by neurologists in LUTH to have ischemic stroke. One hundred and eighty-four control´s blood samples were collected and assayed since their health status are unknown. 100 of the control subject´s blood samples met the research inclusion criteria. Eighty-four contol blood samples were excluded based on dyslipidemia (normolipidemic individuals were used for this study since HL helps in lipid metabolism), HIV, diabetes and other cardiovascular disease risk factors. The control subjects consist of 100 individuals within the same age range and socio-economic status matched with the ischemic stroke patients. Blood samples were obtained in an EDTA and heparin vacutainer bottles from stroke patients and healthy individuals who have been fasting for 12 to 16 hours. The healthy individuals and the stroke patients were grouped separately into three different age groups namely: 46-59, 60-73 and 74-87 years respectively. All the stroke patients and healthy individuals were given consent forms and questionnaires. The result of cigarette smoking, alcohol consumption and history of diabetes were obtained from the questionnaire given to both subjects. (Data not shown).Ethical approval was also obtained from the Research and Ethical Committee of the Institution (University of Lagos Teaching hospital Idi-araba Lagos, Nigeria). Control and stroke subjects not willing to participate in the study were excluded from the study.

2.2 Determination of Blood Pressure

Blood pressure of the ischemic stroke patients and the healthy individuals were measured using mercurial sphygmomanometer on their right arm with subjects in the sitting position after a 5 minutes rest.

2.3 Body Mass Index (BMI) Estimation

BMI of the stroke patients and the healthy individuals were calculated as weight in kilograms divided by the square of height in meters $(kg)/m^2$) using meter rule and weighing balance. Those within the range 18.5-24.9 were grouped as normal while those less than or above this range were categorized underweight or overweight respectivily. Obesity was defined as BMI ≥ $30kgm^{-2}$. The weight was measured to the nearest 0.1kg and the height to the nearest 0.1 cm. Height and weight were measured while subjects were wearing light clothing without shoes and head ties/caps.

2.4 Determination of Hepatic Lipase (HL) Activity

The HL activity of postheparin plasma was carried out by the immunochemical procedure described by Kuusi et al. [27].

2.5 Determination of Plasma Lipid Profile

The total cholesterol (TC), triglyceride (TG) and HDL-cholesterol were assayed using Randox kits. VLDL and LDL- cholestrol were calculated according to Friedewald et al. [35]

VLDL-C =TG/5 and LDL-C=TC- HDL-C –TG/5
Non- HDL-cholesterol = Total cholesterol — HDL-cholesterol

Atherogenic ratios were calculated as follows:

Castellis risk index I (CRI-1) = TC/HDL-C
Castellis risk index II (CRI-11) = LDL-C/HDL-C
HDL-C/LDL-C and TG/HDL-C values were calculated
Atherogenic index of plasma (AIP) = log TG/HDL-C
Atherogenic coefficient (AC) = (TC-HDL-C)/HDL-C

National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATPIII 2001) guideline was referred to define dyslipidemia [36]. Dyslipidemia was defined by the presence of one or more than one abnormal plasma lipid concentration.

2.6 Statistical Analysis

Data are presented as Mean ± SD; GraphPad prism computer software version 5.00 was used for the statistical analysis. Student's 't'test was used to compare SBP, DBP, BMI, lipid profiles and lipoprotein ratios levels for both stroke and control subjects. The correlation of hepatic lipase activity with lipid parameters was determined by Pearson correlation. Bivariate correlation was performed for the control and stroke subjects using HL activity as dependent variable, and lipid parameters as independent variables. Binary logistic regression model for the prediction of ischemic stroke was determined using SPSS version 22. One-way ANOVA Posthoc Turkey´s test was used for comparing significant difference between age groups for the control and the stroke subjects. Two-way ANOVA Posthoc Turkey´s test was also used for comparing the significant difference between both subjects. A P-value < 0.05 was considered statistically significant.

3. RESULTS

The result obtained from the questionnaire shows that ischemic stroke patients are cigarette smokers, high alcohol consumers and they have high history of diabetes when compared to the healthy individuals (Data not shown).

3.1 Hepatic Lipase Activity and Lipid Profiles for Control and Stroke Subjects

HL activity was significantly (P<0.0001) lowered in the stroke subjects compared to the control. Dsylipidemia was also observed in the stroke subjects compared to the control.

3.2 The Correlation Coefficient between BMI, SBP, DBP, Lipid Parameters and HL Activity

Bivariate correlation was performed for both control and ischemic stroke subjects using HL activity as dependent variable, BMI, SBP, DBP, lipid profiles and lipoprotein ratios as independent variables. As shown in Table 3 below, for stroke subjects, positive correlation was obtained between AC (r = 0.2929, R^2=0.08577 and P value = 0.0031), TC/HDL-C (r = 0.2929, R^2=0.08577 and P value =0.0031), LDL-C/HDL-C (r = 0.2878, R^2=0.08283, P value=0.0037), TG/HDL-C (r=0.2029, R^2=0.04116 and P value=0.0429), AIP (r = 0.2234, R^2=0.04991, P value=0.0255) and HL activity. Negative correlation was obtained between HDL-C (r = -0.3137, R^2=0.09840, P value = 0.0015), HDL-C/LDL-C (r = -0.1977, R^2=0.03910, P value = 0.0486), SBP (r = -0.2622, R^2=0.06876, P value = 0.0084) and HL activity. For the control subjects, Negative correlation was obtained between TG (r = -0.2798, R^2= 0.07830 and P value = 0.0048), VLDL-C (r = -0.2798, R^2= 0.07830 and P value = 0.0048), SBP (r = -0.2774, R^2= 0.07698 and P value = 0.0052) and HL activity.

4. DISCUSSION

Stroke is one of the leading causes of death in developed countries and constitutes a major source of disability in persons older than 60 years. Studies have shown that stroke incidences differ by sex, exhibiting the classical "female paradox" phenomenon; while the incidence of stroke is greater among men, women suffer worse outcome from the disease [37-39]. Several studies have highlighted this differential effect of sex on stroke. Di Carlo *et al* [40] reported that women are 41% more likely to have worse disability following stroke than men. Moreover, 60% of stroke deaths in 2008

occurred among women. [41]. Additional studies have also identified differences not only in the risk profiles between the sexes, but also between racial/ethnic groups [42-44].

In our study, we observed significant (P<0.005) higher values of SBP and DBP in older individuals for both control and stroke subjects (Table 1). This signifies that blood pressure may rise as the age increases. Studies have show that in industrialised nations, systolic blood pressure rises continually with age, whereas diastolic blood pressure rises until middle-age and then tends to level-off [45-46]. The stroke subjects had higher (P<0.0001) SBP and DBP compared to the control subjects. Anil Kumar et al. [47] shows that systolic and diastolic blood pressures correlate with increased cardiovascular mortality and stroke in elderly individuals. The stroke subjects had higher BMI values (they are obese) compared to the control subjects (Table 2). Obesity has been shown to be an independent risk factor for cardiovascular mortality and an indirect risk factor because of its effect on hypertension, diabetes, and dyslipidemia [45].

Hepatic lipase enzyme is synthesized in the hepatocytes, secreted, and bound extracellularly to the endothelial cells in hepatic sinusoids. The enzyme plays a key role in remodeling remnant lipoprotein, LDL-C, and HDL-C [48-50]. HL participates in the metabolism of HDL and large triacylglycerol-rich HDL_2, as well as by mediating the unloading of cholesterol from HDL to the plasma membrane of the liver [29,51-54]. Hepatic lipase activities were significantly (30.50±0.3928 µmol/h/ml vs 20.21±0.3706 µmol/h/ml, p value=0.0001) higher in the control subjects compared to the stroke subjects (Table 2). This activity possibly leads to the protective properties (prevention of dyslipidemia) of the enzyme in the control subjects. HL helps in the hydrolysis of phospholipids and TG of chylomicron remnants. The Hydrolysis of chylomicron remnant phospholipids by HL leads to the unmasking of apo E, and thereby enhances binding to apo E-binding receptors [55]. Moreover, HL also acts as a ligand for the binding of chylomicron remnants in the liver [56]. Several studies have showed that a genetic deficiency of HL [57] or inhibition of HL activity [58] is associated with impaired clearance of lipoprotein remnants. The -250G>A, -514C>T, -710T>C and -763A>G polymorphisms in the promoter region of the HL gene account for approximately 20-32% of the variance of HL activity [59]. The four different promoter polymorphisms of the *LIPC* mentioned above are in complete linkage disequilibrium [60-61]. These polymorphisms maybe responsible for the lower activities of HL in all the stroke subjects' studied. Generally, it has been assumed that this association is due to an effect of greater or equal to 1 of the promoter polymorphisms on the rate of transcription of the HL gene. The results of this study showed that dyslipidemia was very high in our stroke subjects compared to the control subjects. This is evidence as there are significant (P<0.0001) higher plasma concentration of total cholesterol, triglyceride, LDL-cholesterol, VLDL-cholesterol and Non-HDL-cholesterol concentrations in the stroke subjects compared to the control subjects (Table 2). We also observed lower HDL-cholesterol in stroke subjects compared to the control subjects (Table 2). The result of this study supports previous research findings [62-65]. The dyslipidemia obtained in the stroke subjects maybe, at least in part, as a result of lower activity of hepatic lipase in the stroke subjects, since the enzyme helps in lipid metabolism.

Many studies have shown the involvement of TG and particularly TG rich lipoproteins in the pathogenesis of cardiovascular disease. TG rich lipoproteins have been shown to induce endothelial dysfunction, enhance monocyte adhesion [66], enter atherosclerotic plaques [67-68] and inhibit reverse cholesterol transport [69]. The potential antiatherogenic properties of HDL-C, includes its mediation of reverse cholesterol transport, in which cholesterol from peripheral tissues is returned to the liver for excretion in the bile [70]. HDL-C has been shown to promote fibrinolysis [71], inhibits Ca^{2+}, and induces procoagulant activity on the erythrocyte membranes [72]. Anti-oxidative property of HDL-C could be as a result of cardio-protective mechanism [73].

Non-HDL-C has been proposed as a good estimator of the atherogenic potential in patients with high TG [74]. The findings of Cui *et al*., has also demonstrated non-HDL-C as a better predictor of CVD mortality than LDL-C during an average follow up of 19 years in 4462 dyslipidemic patients [75]. Interactions between LDL particles, vascular smooth muscle cells, endothelial cells and HDL particles have been described. LDL induced cytotoxicity against human vascular smooth muscle cells and endothelial cells were inhibited by the presence of HDL (76). It can be postulated that low HDL concentration gives reduced protection against LDL toxicity. Studies have shown that an HDL-C

Table 1. Comparism of Hepatic lipase activity, SBP, DBP, BMI, lipid profiles and lipoprotein ratios of control and ischemic stroke subjects

Parameters	Control			Ischemic stroke subject		
	46-59 (years) N=39	60-73 (years) N=44	74 -87 (years) N=17	46-59 (years) N=39	60-73 (years) N=44	74-87 (years) N=17
HL (µmol/h/ml)	$^{a}31.10^{m}$ ±0.51	$^{b}30.18^{n}$ ±0.69	$^{c}28.38^{o}$±0.63	$^{a}22.83^{m}$±0.57	$^{b}21.98^{n}$±0.61	$^{c}19.83^{o}$±0.81
SBP (mmHg)	$^{c}115.36^{o}$±2.31	$^{b}117.73^{n}$ ±3.02	$^{a}121.84^{m}$±2.51	$^{b}167.65^{o}$±2.80	$^{a}171.56^{n}$±3.07	$^{a}173.35^{m}$±2.26
DBP (mmHg)	$^{c}66.86^{o}$±1.56	$^{b}73.08^{n}$ ±1.50	$^{a}78.18^{m}$± 1.71	$^{c}116.63^{o}$± 2.74	$^{b}120.54^{n}$± 1.71	$^{a}124.43^{m}$± 2.88
BMI (Kg/m^2)	^{a} 24.13^{m}±1.69	^{a} 23.69^{mn} ±0.95	^{a} 23.27^{n}±0.89	^{a} 30.36^{m}±0.86	^{a} 30.28^{m}±1.38	^{a} 29.98^{m}±0.26
TC (mg/dl)	$^{ab}171.1^{mn}$±15.67	$^{b}163.2^{n}$ ±13.45	$^{a}177.88^{m}$ ±21.18	^{a} 219 .56^{m}±19.95	^{a} 220.82^{m} ±23.68	^{a} 218.88^{m} ±22.46
TG (mg/dl)	$^{c}87.63^{n}$±3.39	$^{b}89.52^{n}$ ±3.33	$^{a}95.96^{m}$±4.06	$^{a}188.41^{m}$±8.01	$^{b}180.55^{n}$±7.80	$^{ab}185.19^{m}$ ±8.96
HDL-C (mg/dl)	$^{a}116.97^{m}$±3.34	$^{b}99.45^{n}$±3.03	$^{c}91.85^{o}$±2.33	$^{a}64.12^{m}$±3.02	$^{b}51.26^{n}$±1.73	$^{c}48.37^{o}$±1.83
LDL-C (mg/dl)	$^{c}36.04^{o}$±2.59	$^{b}45.01^{n}$ ±3.51	$^{a}65.80^{m}$±3.84	$^{b}117.75^{n}$±6.52	$^{a}113.91^{m}$±7.21	$^{a}133.53^{m}$±6.85
VLDL-C (mg/dl)	$^{c}17.50^{o}$±0.47	$^{b}17.80^{n}$±0.11	$^{a}19.61^{m}$±0.52	$^{a}37.38^{m}$±0.43	$^{b}36.10^{o}$±0.49	$^{a}37.01^{n}$±0.52
Non-HDL-C (mg/dl)	$^{c}54.21^{o}$±2.36	^{b} 63.58^{n}±3.38	$^{a}86.09^{m}$±5.43	$^{b}155.81^{n}$±6.53	$^{a}169.52^{m}$±6.91	$^{a}170.33^{m}$±8.21
AC	$^{c}0.468^{o}$±0.066	$^{b}0.641^{n}$±0.081	$^{a}0.934^{m}$±0.082	$^{c}2.434^{o}$± 0.160	$^{b}3.318^{n}$±0.170	$^{a}3.556^{m}$±0.190
TC/HDL-C	$^{c}1.465^{o}$±0.04	$^{b}1.641^{n}$±0.08	$^{a}1.952^{m}$±0.08	$^{c}3.415^{o}$±0.13	$^{b}4.363^{n}$±0.16	$^{a}4.532^{m}$±0.19
TG/ HDL-C	$^{c}0.747^{o}$±0.023	$^{b}0.902^{n}$±0.019	$^{a}1.052^{m}$±0.034	$^{c}2.921^{o}$±0.048	$^{b}3.526^{n}$±0.092	$^{a}3.849^{m}$±0.088
LDL-C/ HDL-C	$^{c}0.303^{o}$±0.046	$^{b}0.428^{n}$±0.051	$^{a}0.706^{m}$±0.053	$^{c}1.859^{o}$±0.086	$^{b}2.618^{n}$±0.154	$^{a}2.76\ 8^{m}$±0.165
HDL-C/ LDL-C	$^{a}3.451^{m}$±0.031	$^{b}2.337^{n}$±0.026	$^{c}1.435^{o}$±0.016	$^{a}0.575^{m}$±0.041	$^{b}0.396^{n}$±0.023	$^{b}0.379^{n}$±0.043
AIP	^{c}-0.134^{o}±0.011	^{b}-.0438^{n}±0.015	$^{a}0.023^{m}$±0.018	$^{c}0.466^{o}$ ±0.008	$^{b}0.549^{n}$±0.013	$^{a}0.587^{m}$±0.027

Data are presented as Mean ± SD (n=200). HL, hepatic lipase activity; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein-cholesterol; Non-HDL-C, Non-high-density lipoprotein-cholesterol, AC, atherogenic index; TC/HDL-C, total cholesterol/ high-density lipoprotein-cholesterol; LDL-C /HDL-C, low-density lipoprotein-cholesterol/ high-density lipoprotein-cholesterol; TG/HDL-C, triglyceride/ high-density lipoprotein-cholesterol; AIP, atherogenic index of plasma; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure. One-way ANOVA Posthoc Turkey´s test was used for comparing significant difference between age groups for the control and the stroke subjects.. a=highest, b= medium, c=lowest. Those groups that have the same letters are not statistically significant (P>0.05) while those that have different letters are statistically significant (P<0.05). Two-way ANOVA Posthoc Turkey´s test was also used for comparing the significant difference between both subjects. m=highest, n= medium, o=lowest. Those groups that have the same letters are not statistically significant (P>0.05) while those that have different letters are statistically significant (P<0.05). A P<0.05 was considered statistically significant

associated paraoxonase was proved to give protection against LDL oxidative modifications (77-78). These complex interactions might participate in atherosclerosis development and it might be that in our stroke subjects, the presence of low HDL-C concentration participates in preclinical development of atherosclerosis.

In an attempt to optimize the predictive capacity of lipid parameters in risk evaluation, several lipoprotein ratios were defined. The ability of these lipoprotein ratios to predict cardiovascular disease compared to single lipid markers is of particular clinical relevance and can be possibly explained by association of lipoprotein ratios with a cluster of cardiovascular risk factors that are at least in part unrelated to cholesterol metabolism [31]. The control subjects showed signifinantly ($P<0.0001$) lower value for atherogenic coefficient, Castelli risk index-I, Castelli risk index- II, TG/HDL-C, and atherogenic index of plasma when compared with the stroke subjects (Table 2). The control subjects had higher plasma concentration of HDL-C/LDL-C compared to the stroke subjects. We observed significant ($P<0.0001$) decrease in HL activity, HDL-C and HDL-C/LDL-C ratio levels for both control and stroke subjects as their age increases. This is an indication that these parameters decreased with aging in our study (Table 1). Other biochemical parameters like: SBP, DBP, Non-HDL-C, AC, TC/HDL-C, TG/HDL-C, LDL/HDL-C and AIP levels increased significantly ($P<0.0001$) with aging (Table 1). This indicates that these parameters increased with aging as shown in our study. Other studies have shown that these dyslipidemia are responsible for cardiovascular disease. In patients with recent stroke or TIA and no coronary heart disease, only lower baseline HDL-C predicted the risk of recurrent stroke (79). Baseline HDL-C, triglycerides, and LDL/HDL ratio were associated with stroke plus myocardial infarction and vascular death from their study. They also show that only baseline HDL-C and LDL/HDL ratio were associated with an outcome of ischemic stroke and 13.7 mg/dL increment in HDL-C was associated with a 13% reduction in the risk of ischemic stroke and doubling of LDL/ HDL ratio was associated with a 31% increase in the risk of ischemic stroke [79].

The predictive level and significant of correlation between HL activity and lipid parameters were assessed by regression analysis taking HL as dependent variables and lipid parameters as independent variables for both the control and stroke subjects.

Table 2. Comparing hepatic lipase activity, BMI, SBP, DBP and lipid parameters of control and ischemic stroke subjects

Parameters	Control	Stroke subjects	P value
HL (µmol/h/ml)	30.50 ± 0.3928	20.21 ± 0.3706	0.0001
SBP (mmHg)	116.8 ± 1.692	175.8 ± 1.844	0.0001
DBP (mmHg)	72.55 ± 0.8754	122.1 ± 0.9772	0.0001
BMI (Kg/m^2)	23.50 ± 0.2342	30.90 ± 0.3573	0.0001
TC (mg/dl)	168.4 ± 1.796	224.6 ± 2.889	0.0001
TG (mg/dl)	89.83 ± 1.265	190.1 ± 1.872	0.0001
HDL-C (mg/dl)	100.9 ± 0.9951	58.85 ± 0.9072	0.0001
LDL-C (mg/dl)	48.40 ± 1.519	127.8 ± 2.799	0.0001
VLDL-C (mg/dl)	17.97 ± 0.2530	38.03 ± 0.3744	0.0001
Non-HDL-C (mg/dl)	67.42 ± 2.080	165.8 ± 2.820	0.0001
AC	0.6863 ± 0.02792	2.898 ± 0.07564	0.0001
TC/HDL-C	1.686 ± 0.02792	3.898 ± 0.07564	0.0001
TG/ HDL-C	0.8971 ± 0.01474	3.300 ± 0.05506	0.0001
LDL-C/ HDL-C	0.4912 ± 0.01842	2.238 ± 0.06921	0.0001
HDL-C/ LDL-C	2.358 ± 0.1074	0.4868 ± 0.01403	0.0001
AIP	-0.05282 ±0.00705	0.5128 ± 0.007015	0.0001

Data are presented as Mean ± SD (n=200). HL, hepatic lipase activity; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; VLDL-C, very low density lipoprotein-cholesterol; Non-HDL-C, NON-high density lipoprotein-cholesterol, AC, atherogenic index; TC/HDL-C, total cholesterol/ high density lipoprotein-cholesterol; LDL-C /HDL-C, low density lipoprotein-cholesterol/ high-density lipoprotein-cholesterol; TG/HDL-C, triglyceride/ high density lipoprotein-cholesterol; HDL-C/LDL-C, high density lipoprotein-cholesterol /low density lipoprotein-cholesterol; *AIP, atherogenic index of plasma; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; student 't' test was used to compare the significance of the difference in the mean values between the control and ischemic stroke subjects using graphpad prism software. A P<0.05 was considered statistically significant*

Table 3. Correlation between hepatic lipase activity and lipid parameters for both control and stroke subjects

Variable	Hepatic lipase activity of control subject (µmol/h/ml)			Hepatic lipase activity of stroke subject (µmol/h/ml)		
	r	R^2	P value	R	R^2	P value
TC	-0.1618	0.02617	0.1079	0.00826	0.0000683	0.9350
TG	-0.2798	0.07830	0.0048	-0.1886	0.03557	0.0602
HDL-C	-0.1622	0.02631	0.1069	-0.3137	0.09840	0.0015
LDL-C	0.02600	0.0006758	0.7974	0.1354	0.01834	0.1791
VLDL-C	-0.2798	0.07830	0.0048	-0.1886	0.03557	0.0602
Non- HDL-C	-0.06205	0.003850	0.5397	0.1094	0.01196	0.2788
AC	0.01048	0.0001098	0.9176	0.2929	0.08577	0.0031
TC/HDL-C	0.01048	0.0001098	0.9176	0.2929	0.08577	0.0031
LDL-C/ HDL-C	0.06769	0.004583	0.5034	0.2878	0.08283	0.0037
HDL-C/ LDL-C	-0.08699	0.007568	0.3894	-0.1977	0.03910	0.0486
TG/HDL-C	-0.1339	0.01792	0.1842	0.2029	0.04116	0.0429
AIP	-0.1642	0.02697	0.1025	0.2234	0.04991	0.0255
BMI (Kg/m^2)	-0.1796	0.03226	0.0738	-0.05396	0.002911	0.5939
SBP (mmHg)	-0.2774	0.07698	0.0052	-0.2622	0.06876	0.0084
DBP (mmHg)	-0.07196	0.005178	0.4768	-0.1627	0.02646	0.1059

Data are presented as Mean ± SD (n=200). TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; VLDL-C, very low density lipoprotein-cholesterol; Non-HDL-C, Non-high-density lipoprotein-cholesterol, AC, atherogenic index; TC/HDL-C, total cholesterol/high density lipoprotein-cholesterol; LDL-C/HDL-C, low density lipoprotein-cholesterol/high density lipoprotein-cholesterol; TG/HDL-C, triglyceride/high density lipoprotein-cholesterol; HDL-C/LDL-C, high density lipoprotein-cholesterol /low density lipoprotein-cholesterol;AIP, atherogenic index of plasma; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure and A P<0.05 was considered statistically significant

Table 4. Logistic regression model for the prediction of ischemic stroke

	Log (Odd ratio)	Std error	Wald (t-test)	P-value	Odd ratio	95% C.I. for odd ratio		
						Lower	Upper	
HL	-0.683	0.101	46.129	0.000	0.505	0.415	0.615	S
TC	0.081	0.011	59.009	0.000	1.084	1.062	1.107	S
TG	0.005	0.001	21.188	0.000	1.005	1.003	1.007	S
HDL-C	-.436	0.143	9.258	0.002	0.647	0.488	0.856	S
LDL-C	0.128	0.022	35.211	0.000	1.137	1.090	1.186	S
NonHDL	0.101	0.017	34.355	0.000	1.106	1.069	1.144	S
VLDL-C	0.025	0.005	22.296	0.000	1.025	1.014	1.035	S
AC	7.327	1.898	14.908	0.000	1520.378	36.873	62688.791	S
TC/HDL	7.327	1.898	14.908	0.000	1520.378	36.873	62688.791	S
LDL/HDL	20.011	11.514	3.020	0.000	490488439.6	0.078	3.102E+18	S
TG/HDLC	34.071	2838.416	0.000	0.990	6.261E+14	0.000	VeryLarge	NS
A1P	138.244	12339.876	.000	0.991	1.093E+60	0.000	VeryLarge	NS
HDL/LDL	-0.902	0.137	43.578	0.000	0.406	0.312	0.530	S
BMI	0.851	0.118	52.444	0.000	2.343	1.861	2.950	S
SBP	0.236	0.049	23.557	0.000	1.267	1.151	1.394	S
DBP	0.542	0.213	6.501	0.011	1.720	1.134	2.610	S

The test above shows that TG/HDL-C and A1P are not significant because their P-values are greater than 5% level of significance. The remaining risk factors are significant at 5% level. This shows that the factors are significant risk factors for stroke that most be taken into consideration. Among the significant risk factors, LDL/HDL (0R=490488439.6, 95%CI=0.078 - 3.102E+18, P=0.000) has the highest odd of having stroke, closely followed by AC and TC/HDL. Subjects are the respondent variable: stroke=1 and control= 0

The bivariate correlation result showed that for the stroke subjects, R^2 value of 0.08577, 0.08577, 0.08283, 0.04116 and 0.04991 indicate 8.6%, 8.6%, 8.3%, 4.1% and 5.0% variation in the HL activity were due to AC, TC/HDL, LDL/HDL, TG/HDL and AIP respectively. There were no correlation between TC, TG, LDL-C, other lipid parameters and HL activity (Table 3). Negative correlation was obtained between HDL-C, HDL-C/LDL-C, SBP and HL activity. For the control subjects, we observed negative correlation between TG, VLDL, SBP and HL activity.

In a final logistic regression model for the prediction of ischemic stroke, risk factors like: HL, TC, TG, HDL-C, LDL-C, VLDL-C, Non-HDL-C, AC, TC/HDL-C, LDL/HDL, HDL/LDL, BMI, SBP and DBP all predicted ischemic stroke in our study (Table 4). LDL-C/HDL-C emerged as an independent risk factor (0R=490488439.6, 95%=0.078-3.102E+18 and P=0.000) for the development of ischemic stroke. Amerenco et al [79] shows that doubling of LDL/ HDL ratio was associated with a 31% increase in the risk of ischemic stroke. The results of our study support the fact that LDL-C/HDL-C ratio is superior to other lipid parameters as a predictor of ischemic stroke. Adrià Arboix's study shows that cardiovascular risk factors profile differs according to the different subtypes of ischemic stroke. Hypertension, atrial fibrillation and diabetes mellitus are the most common risk factors for acute cerebrovascular events. Novel risk factors such as sleep-disordered breathing, inflammatory markers or carotid intima-media thickness have also been identified [80].

5. CONCLUSION

In conclusion, hepatic lipase activities were significantly higher in control compared to the stroke subjects. Higher BMI values and dyslipidemia were obtained in the ischemic stroke subjects and LDL-C/HDL-C is the major risk factor for the development of ischemic stroke.

CONSENT

Authors declare that written informed consents were obtained from healthy subjects and patients before their participation in the study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate Institutional ethics review committee and have therefore been performed in accordance with the ethical standards laid down in the ethics review committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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