ROLE OF NON-HIGH-DENSITY LIPOPROTEIN CHOLESTEROL IN CEREBROVASCULAR ACCIDENTS
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ABSTRACT

BACKGROUND
The role of non-high-density cholesterol (non-HDL-C) in cardiovascular events and cerebrovascular events remains a subject of controversy. We wanted to evaluate the role of non-HDL-C in stroke.

METHODS
Our cross-sectional study enrolled 100 participants with acute cerebrovascular accident (CVA) excluding traumatic CVA and CVA due to vasculitis. Institutional ethics committee approved the study and written informed consent was obtained from all study participants. Collected data included history, socio demographic parameters, examination findings and laboratory parameters. Non-HDL-C was calculated by deducting HDL-C from TC. Tests of significance were independent sample t test and Chi square test and a p <0.05 was considered statistically significant.

RESULTS
The mean age of stroke was ~64 years, mean systolic and diastolic blood pressure were in the prehypertensive range. Significant association of serum LDL and non-HDL with ASCVD risk categorization was observed.

CONCLUSIONS
Increase in incidence of stroke among young was observed with higher prevalence among males. Increasing burden of prehypertension and diabetes mellitus was observed among stroke patients. 20% participants had high serum non-HDL with normal serum total cholesterol. Our study demonstrates the significance of non-HDL in acute stroke and might be a better predictor when used along with conventional investigations. Further studies on larger samples are required to demonstrate the usefulness of this parameter for predicting cerebrovascular accidents.

KEYWORDS
Stroke, Non-HDL, ASCVD Risk, LDL

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stroke incidence to people aged less than 65 years and this has been described as due to epidemic rise in cardiovascular diseases in Russia, China and India.9-12 12% of strokes in India occur in less than 40 years,12 and these account for considerable morbidity and healthcare expenditure.

Complex relationship exists between serum lipids and stroke. Direct relationship exists between ischemic stroke and lipids predominantly the atherosclerotic subtype of ischemic stroke.13 whereas lower cholesterol levels are associated with hemorrhagic stroke and small vessel disease. The strongest association has been reported for low density lipoprotein (LDL-C) and total cholesterol (TC). Non High density lipoprotein cholesterol (non-HDL-C) is the arithmetic sum of all lipoproteins except HDL-C which includes chylomicron, Very Low Density Lipoprotein (VLDL) and their remnants, intermediate density lipoprotein (IDL), LDL-C and lipoprotein A.14 Very little attention is given to non-HDL-C as a predictor for coronary artery disease, stroke and atherosclerosis though both European and American Cardiological society emphasizes otherwise. Non-HDL-C is to be considered next to elevated LDL levels as a predictor of many cardiovascular diseases and the goal is to maintain non-HDL-C less than 130 mg/dl in patients with coronary heart disease (CHD) or CHD risk equivalent. The increase in non-HDL-C by 1 mg/dl increases the risk of death due to cardiovascular events by 5% and has been shown to be a better predictor of cardiovascular events compared to conventional risk factors.15 A 1.5 to 2.5 times higher risk of cardiovascular events among diabetics with elevated non-HDL-C has also been observed.15 A 1% reduction of non-HDL-C was associated with a 1% reduction in cardiovascular disease in patients treated with pharmacological agents.16 Since a large number of controversies exist in the use of non-HDL-C for routine investigations our study aims at assessing the use of this parameter as a predictor of cerebrovascular accidents (CVA).

METHODS

The present cross-sectional study enrolled 100 participants aged 18 years or above with acute CVA admitted in General Medicine department of Aarupadai Veedu Medical College and Hospital during a period from September 2016 to September 2018. Participants with traumatic CVA and CVA secondary to vacuities were excluded from the study. The study was approved by institutional ethics committee and written informed consent was obtained from all study participants. Data was collected in case record forms and included the history (cigarette smoking, alcohol consumption, hypertension, diabetes mellitus and family history), socio demographic parameters (age, gender, educational status, occupation and socioeconomic status), examination findings (blood pressure, side of involvement) and laboratory parameters (TC, LDL-C, HDL-C, VLDL and triglycerides (TG), fasting plasma glucose (FPG), 2 hour post prandial glucose (2h-PPG), blood urea, serum creatinine and serum electrolytes). TC, HDL-C and TG were measured after overnight fasting. LDL was calculated by Fried Wald formula17 \[ \text{LDL} = \text{TC-HDL-C-(TG/5)} \]. Non-HDL-C was calculated by deducting HDL-C from TC. Stroke was assessed based on clinical symptoms, examination and findings of radiological imaging. Values are expressed as mean (standard deviation (SD)) and frequency (%) and are rounded off to nearest decimal. Means of numerical variables were compared between groups using independent sample t test and categorical variables were compared for association using Chi square test. Odds ratio was used to determine association between groups with 95% confidence intervals. A p <0.05 was considered statistically significant.

RESULTS

Among the participants, 63% (n=63) were males and 37% (n=37) were females. Baseline parameters of study participants is demonstrated in table 1. 41% (n=41) participants were over 70 years, 27% (n=27) were aged 60-69 years, 19% (n=19) were aged 50-59 years and 4% (n=4) participants had stroke at less than 40 years.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>64.2 (14.2)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>139.9 (25.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>88.6 (15.2)</td>
</tr>
<tr>
<td>Blood urea (mg/dL)</td>
<td>37.8 (28.4)</td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9 (0.7)</td>
</tr>
<tr>
<td>Serum sodium (mg/dL)</td>
<td>134.8 (5.8)</td>
</tr>
<tr>
<td>Serum potassium (mg/dL)</td>
<td>3.9 (0.5)</td>
</tr>
<tr>
<td>Serum chloride (mg/dL)</td>
<td>101.3 (6.1)</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>145.3 (83.1)</td>
</tr>
<tr>
<td>2h-PPG (mg/dL)</td>
<td>177.3 (96.1)</td>
</tr>
<tr>
<td>Serum TC (mg/dL)</td>
<td>197.2 (34.2)</td>
</tr>
<tr>
<td>Serum LDL-C (mg/dL)</td>
<td>127.3 (34.5)</td>
</tr>
<tr>
<td>Serum HDL-C (mg/dL)</td>
<td>41.3 (8.7)</td>
</tr>
<tr>
<td>Serum TG (mg/dL)</td>
<td>139.2 (60.3)</td>
</tr>
<tr>
<td>Serum VLDL (mg/dL)</td>
<td>28.4 (13.1)</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>156.1 (33.6)</td>
</tr>
</tbody>
</table>

Table 1. Baseline Parameters of Study Participants

Among study participants, 52% (n=52) were manual labourers and 40% (n=40) were unemployed. 52% (n=52) participants had right sided cerebrovascular accident. 84% (n=84) participants had one or more established risk factor for CVA. Gender based comparison of parameters showed no significant difference in age groups (p=0.6), side of involvement (p=0.8) and type of CVA (p=0.1). The risk factors associated with CVA were diabetes mellitus (65%), systemic hypertension (50%), alcoholism (36%), smoking (30%) and coronary artery disease (1%). 6% (n=6) had haemorrhagic CVA and 94% (n=94) had ischemic CVA. No association was observed between age groups and gender (p=0.6), gender and side of involvement (p=0.8), type of CVA and gender (p=0.1). Gender based comparison of baseline parameters showed significantly higher systolic (p=0.02) and diastolic blood pressure (p=0.003) among females. Significantly higher serum creatinine (p=0.01) and serum potassium (p=0.04) among participants with ischemic stroke was observed. 63% (n=63) participants were having uncontrolled serum LDL-C and 39% (n=39) participants were having uncontrolled non-HDL-C. Significantly higher age (p=0.001), FPG (p=0.001), 2h-PPG (p=0.001), serum TC (p=0.002) and serum non-HDL-C (p=0.004) was observed among participants with high LDL-C. Significantly
higher VLDL (p=0.001) and TG (p=0.005) was observed among participants with normal serum LDL-C. Significantly lower age (p<0.001), systolic (p=0.006) and diastolic blood pressure (p<0.006) were observed among participants with high non-HDL-C and significantly higher serum TC (p<0.001) and serum LDL-C (p<0.001) were observed among participants with high non-HDL-C. Significant association of age with serum LDL-C (p=0.001, table 2) and serum non-HDL-C (p=0.001, table 3) was observed. Significant association between side of involvement and serum LDL-C was observed (p=0.04; OR: 0.4, 95% CI 0.2-0.9), hypertension and serum non-HDL-C (p=0.01; OR: 3.1, 95% CI 1.3-7.1), diabetes mellitus and serum LDL-C (p<0.001; OR: 0.1, 95% CI 0.04-0.4), diabetes mellitus and serum non-HDL-C (p<0.001; OR: 9, 95% CI 2.9-28.6) were observed. Significant association was observed between serum TC and non-HDL-C (p<0.001; OR: 0.1, 95% CI 0.06-0.4). The association of ASCVD risk categorization and serum LDL-C is demonstrated in table 2. Significant association was observed between groups (p<0.001) probably indicating higher proportion of participants with high serum LDL-C among participants with 10-year risk of cardiovascular event of >20%.

<table>
<thead>
<tr>
<th>ASCVD Risk Category</th>
<th>Serum LDL</th>
<th>Within Reference Range (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10% (n=27)</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>10-20% (n=15)</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>&gt;20% (n=58)</td>
<td>51</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2. Association of ASCVD Risk Categorization and Serum LDL-C

<table>
<thead>
<tr>
<th>ASCVD Risk Category</th>
<th>Serum Non-HDL-C</th>
<th>Within Reference Range (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10% (n=27)</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>10-20% (n=15)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>&gt;20% (n=58)</td>
<td>9</td>
<td>49</td>
</tr>
</tbody>
</table>

Table 3. Association of ASCVD Risk Categorization and Serum Non-HDL-C

Significant association was observed between groups (p<0.001), probably indicating higher proportion of participants with normal serum non-HDL-C levels having a 10-year cardiovascular risk score of >20%. No association was observed between serum TG and serum LDL-C (p<0.4), serum triglycerides and non-HDL-C (p=0.9). No association of serum HDL with serum LDL and serum non-HDL was observed (p=0.7 & 0.3 respectively). No association of gender with serum LDL (p=0.3; OR: 1.5, 95% CI 0.7-3.5) and serum non-HDL (p=0.8; OR: 0.9, 95% CI 0.4-2) was observed. No association of side of involvement with serum non-HDL (p=0.2; OR: 1.5, 95% CI 0.7-3.3), hypertension with serum LDL (p=0.6; OR: 0.5, 95% CI 0.2-1), coronary artery disease with serum LDL (p=1; OR: 0.6, 95% CI 0.5-0.7), coronary artery disease with serum non-HDL (p=1; OR: 0.6, 95% CI 0.5-0.7) was observed. No association of smoking with serum LDL categorization (p=1; OR: 0.6, 95% CI 0.5-0.7) and serum non-HDL categorization (p=1; OR: 0.6, 95% CI 0.5-0.7) was observed. No association of alcoholism with serum LDL (p=0.8; OR: 1.1, 95% CI 0.5-2.6) and serum non-HDL (p=0.7; OR: 0.8, 95% CI 0.4-1.9) was observed. No association of type of cerebrovascular accident with serum LDL (p=0.1; OR: 0.3, 95% CI 0.05-1.6) and serum non-HDL (p=0.2; OR: 3.4, 95% CI 0.6-19.4) was observed.

**DISCUSSION**

Our prospective cross-sectional study enrolled 100 participants admitted with cerebrovascular accident at Aarupadai Veedu Medical College, Pondicherry, and Tamil Nadu in a period of 2 years. The mean ages of the participants were ~ 64 years. Reports of reduction in the mean age of stroke patients from 71 years to 69 years in the time period 1993 to 2005 could be the possible explanation to this lower mean age. The mean blood pressure of study participants were in the prehypertensive range (~139/88) which could be due to the increase in prevalence of hypertension and prehypertension among rural and urban population alike. The mean FPG and 2h-PPG of the study participants were in the diabetic (~145 mg/dL) and prediabetic (~177 mg/dL) range indicating the increasing prevalence of the global pandemics diabetes mellitus and prediabetes. The mean lipid parameters of the study participants were within normal range. This is a relief from the reports of ever-increasing prevalence of lifestyle disorders. Predominant proportion of the study participants has jobs that require physical exertion which could explain this finding. Maximum proportion of participants were aged ≥60 years which is in concurrence with previous reports of incidence of >70% stroke in >65 year old. 63% of study participants were males which is similar to previous reports of higher incidence of stroke among males. Predominant proportion of participants were manual labourers or unemployed (92%), Tamil Nadu being the state that has the highest unemployment rate substantiates this finding. Higher proportions of participants were having symptoms on the right side (52%) indicating left hemisphere involvement which could corroborate the reports of higher rate of recognition of left sided.

Stroke compared to right sided stroke. Most of the participants presented with unilateral upper and lower limb weaknesses (95%), 3% participants presented with both lower limb weakness. Lower limb involvement in stroke has been described in 4% patients with stroke. 84% of participants had risk factors for stroke which included hypertension (50%), diabetes mellitus (65%), smoking (30%), alcoholism (36%) and CAD (1%). Hypertension has been reported in 84% participants with acute stroke and diabetes mellitus in 16% participants with stroke. Both smoking and alcoholism has been described as individual risk factors for stroke. The lower incidence of hypertension and higher incidence of diabetes mellitus could be due to the regional difference in prevalence of these lifestyle disorders. 6% of the participants had haemorrhagic stroke which has been described in 10-20% of all stroke patients. The lower proportion of haemorrhagic stroke could be due to the early diagnosis and management of the risk factors associated with haemorrhagic stroke.
Comparison of baseline parameters between gender showed significantly higher systolic (p=0.02) and diastolic blood pressure (p=0.003) among female participants though hypertension is far less likely to occur among females.33 This could be explained on the basis of other co-morbidities such as obesity and insulin resistance which are contributors to systemic hypertension and has not been evaluated in our study. Haemoglobin was significantly higher among male participants (p=0.01) which is a normal physiological finding due to the direct effect of sex hormones.34 No other parameter showed significant difference in gender. Between types of cerebrovascular accidents, participants with ischemic CVA had significantly higher serum creatinine (p=0.01) and serum potassium (p=0.04), though transient renal impairment has been observed more commonly in haemorrhagic stroke.35 This could be an incidental finding or could be due to the enrolment of higher proportion of participants with pre-existing renal impairment.

63% participants had high LDL levels, elevated LDL has been associated with increased risk of ischemic stroke.36 Non-HDL levels were high among 39% participants, which also has been depicted as an individual risk factor for stroke.37 Between participants with and without serum LDL control, significantly higher age (p<0.001), FPG (p<0.001), 2-h PPG (p=0.001), serum total cholesterol (p=0.002) and serum non-HDL (p=0.004) was observed. The increase in LDL levels with age has been previously described as due to reduced catabolism due to reduced expression of LDL receptors with increasing age.38 Higher fasting and post prandial blood glucose levels among participants with high LDL could be based on the bidirectional association of dyslipidaemia and metabolic syndrome.39 High serum non-HDL has been previously described in participants40 with elevated LDL cholesterol and an associated hypercholesterolemia has been described.40 Since non-HDL is calculated by subtracting HDL from total cholesterol, the elevation of LDL with elevation of total cholesterol would mean elevation of non-HDL. Participants having serum LDL within reference range had higher serum triglycerides and serum VLDL. Serum triglyceride levels could be influenced by diet (high carbohydrates,41 alcohol42 and insulin resistance42) and would possibly explain this elevation. The exact mechanism of elevation of VLDL among participants with normal serum LDL could not be explained on the basis of available literature and this finding requires further evaluation. Participants with normal serum non-HDL were significantly older (p<0.001) and higher systolic (p=0.006) and diastolic (p=0.006) blood pressure. Participants with elevated non-HDL were having significantly higher total cholesterol (p<0.001) and serum LDL (p<0.001). Previous reports suggest that increasing age produces better control of serum non-HDL43. The association between blood pressure and non-HDL cholesterol requires further evaluation, since previous studies have reported a non-significantly higher proportion of hypertensive among participants with normal serum non-HDL.43 Published literature suggests an association between serum LDL and non-HDL similar to that described in our study.43 The relationship between total cholesterol and serum non-HDL has not been described clearly and requires further evaluation. Significant association of age with serum LDL (p<0.001) and non-HDL (p=0.001) was observed with higher proportion of participants aged >70 years with high LDL and non-HDL levels within reference range. Reduced catabolism of LDL with increasing age could be postulated as the reason for this finding38 and reduced non-HDL among elderly could be the reason for this association.43

Lower odds of encountering left sided cerebrovascular accident among participants with high serum LDL were observed. This association requires further evaluation since it has not been described before. Higher odds of encountering high non-HDL among non-hypertensive participants were observed. Hypertension has been described as a risk factor for ischemic44 and haemorrhagic stroke.32 In the absence of this established risk factor, non-HDL cholesterol should be considered as a predominant risk factor.37 Lower odds of encountering high serum LDL among non-diabetics was observed, the typical lipid abnormality observed in diabetes mellitus and insulin resistance is high triglyceride low HDL dyslipidaemia,45 which explains this finding. Higher odds of encountering high non-HDL among non-diabetics were observed although contradicting reports have been published.46 This finding requires further evaluation. Significantly higher proportion of participants with high serum LDL and non-HDL under reference range among participants with ASCVD risk >20% was observed. This could be since ASCVD risk categorization uses serum LDL and not serum non-HDL to calculate cardiovascular risk. Lower odds of encountering high serum LDL among participants with normal total cholesterol were observed. This is a normal finding since total cholesterol includes serum LDL as a component.45 Lower odds of encountering high non-HDL among participants with normal serum cholesterol were observed. This could indicate the positive association between non-HDL and serum total cholesterol and its relationship with stroke. This association requires studies of larger samples to determine the exact strength of this association. No association of serum triglycerides with serum LDL and non-HDL was observed though higher TG levels were reported to be associated with percentage atheroma volume and subsequent cardiovascular events.47 Lower odds of encountering high serum LDL among participants with high non-HDL was observed indicating the necessity of using non-HDL as an independent risk predictor for cerebrovascular accidents and other cardiovascular events.

CONCLUSIONS
Increase in incidence of stroke among young was observed with higher prevalence among males with diabetes mellitus being the most prevalent risk factor. Increasing burden of prehypertension and diabetes mellitus was observed among stroke patients. High serum LDL and non-HDL were observed among 63% and 39% participants respectively. 20% participants had high serum non-HDL with normal serum LDL and 18% participants had high serum non-HDL
with normal serum total cholesterol. Our study demonstrates the significance of non-HDL in acute stroke. It might be a better predictor when used along with conventional investigations. Further studies on larger samples are required to demonstrate the usefulness of this parameter for predicting cerebrovascular accidents.

REFERENCES


