

Role of non-HDL cholesterol in assessing the risk of ischemic stroke on established coronary artery disease patients who were on atorvastatin therapy

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Abstract

Atherosclerosis and its sequel are the leading causes of mortality in this world. With increasing prevalence of sedentary life habits and fast food culture early onset obesity are increasing in prevalence. Because of widespread awareness there is increasing use of statin therapy. But still the risk of coronary and cerebrovascular events has not come down. This study was conducted for analysing lipids beyond LDL. The age ranges from 40 to 80 and the study included both sexes. The study was approved by institutional ethics committee. The risk factors associated with, both modifiable like cigarette smoking, alcohol consumption, hypertension, diabetes mellitus and obesity (BMI) and non-modifiable like age, sex, family history was taken into consideration. The risk factors smoking and alcohol were found out by careful history taking. The risk factors DM and HT were detected by past medical history and laboratory routine investigation and BP measurement. The cut off for non HDL cholesterol is generally thirty mg/dl more than LDL cut off values. 38 % of controls had their non-high density lipoprotein cholesterol in the optimal range. But only 20 % of cases had their non HDL cholesterol in the optimal range. The mean non HDL cholesterol among cases is 160.04 mg/dl. The mean HDL cholesterol among controls is 136.64 mg/dl.

Keywords: Non HDL Cholesterol, Ischemic Stroke, Coronary Artery Disease Fo

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INTRODUCTION

For decades the role of LDL cholesterol in predicting the risk of coronary and cerebrovascular events has been well established. It is now clear that LDL is not the only atherogenic particle. But other particles that contain apoprotein B such as VLDL, VLDL remnants, IDL, and Chylomicron remnants are important. This is reflected in the non HDL cholesterol value which is a simple

measure. It does not require fasting specimen. ¹It is calculated by subtracting total cholesterol from HDL cholesterol. Patients on statin therapy have relatively low LDL cholesterol but still a significant number of patients develop a second coronary or cerebrovascular event. In those patients other parameters in lipid profile such as triglycerides, low HDL cholesterol, & lipoprotein a and other remnant lipoproteins are important. The terminology non HDL cholesterol which includes all cholesterol other than HDL has a significant role in assessing the second risk for subsequent development of coronary or cerebrovascular events in statin treated individuals. The study was conducted to stress the importance of other parameters of lipid profile in bringing down the ischemic events.²

Atherosclerosis and its sequel are the leading causes of mortality in this world. With increasing prevalence of sedentary life habits and fast food culture early onset obesity are increasing in prevalence. Because of widespread awareness there is increasing use of statin

therapy. But still the risk of coronary and cerebrovascular events has not come down. This study was conducted for analysing lipids beyond LDL.

Garg *et al.*,³ conducted a study to recognise the lipid parameter which has high levels of relation with both coronary artery disease and metabolic syndrome. They also had an aim of analysing the association of non HDL cholesterol and metabolic syndrome in particular among people residing in north India.

Their study included: One hundred and thirteen Coronary artery disease patients & involved one hundred and forty non-coronary artery disease patients as controls between the ages thirty five and seventy five years. Both cases and controls were matched for race and geography.

Consent was obtained from both the controls and cases in writing. The study identified cases on the basis of history and standard investigations. They measured Height, weight, waist and hip circumferences, blood pressures (systolic and diastolic) and lipid profile.

The study concluded that Sixty nine among 113 (61.06%) of coronary artery disease patients and fifty two among one hundred and thirty (37.1%) of non-coronary artery disease patients had metabolic syndrome.

The CAD patients were identified based on their medical diagnostic history. Height, weight, waist and hip circumferences, blood pressures (systolic and diastolic) and lipid profile were measured for all the subjects. Age standardized presence of abnormalities in coronary artery disease was in the following order. Abdominal obesity had the best correlation followed by non-High density lipoprotein cholesterol which was followed by systolic blood pressure.

The triglycerides, total cholesterol values and low density lipoproteins and HDL cholesterol had lesser significance and had decreasing value of correlation in that order. This specifies the role played by non-high density lipoprotein cholesterol by acting as a screening measure to identify patients with metabolic syndrome to assess their coronary vascular risk.

Sigedel *et al.*,⁴ conducted a study to assess if non HDL cholesterol was an important measure in assessing CAD risk. Total cholesterol values and low density lipoprotein cholesterol values are being used as correlative markers for many years. But many studies have reported non-High density cholesterol as an important and easy measure, since non High density lipoprotein can be calculated by deducting High density cholesterol from total amount of cholesterol.

It was a cross sectional study. Fifty one myocardial infarction patients and same number of controls clinical history electro and echo cardiography and enzyme analysis were used to diagnose myocardial infarction.

Non HDL cholesterol values were obtained by deducting high density lipoprotein from total cholesterol.

The results were statistically analysed. Forty two myocardial infarction cases had abnormal lipid profile in contrast to twenty of the controls. The study concluded that High density lipoprotein cholesterol had a better correlation followed by non-High density lipoprotein cholesterol. In this study non HDL cholesterol had a p value of 0.02 and low density lipoprotein had a p value of 0.05. The study concluded that HDL Cholesterol and non-high density cholesterol serve as a better measure than low density lipoprotein.

Vaccaro *et al.*,⁵ A study was conducted by Vaccaro et al to find the relationship between lifestyle changes advised by medical faculty & non high density lipoprotein cholesterol values. The study was done in United States among various. It collected data from national surveys. It concluded that minority population of UNITED STATES had received more dietary advice. Eighty per cent followed the advice. Those who were then practising weight reducing measures had low non high density cholesterol values. It stressed upon greater motivation to follow these goals persistently.

METHODOLOGY

Number of study groups: two

Group 1 CASES: 50 patients with a history of coronary artery disease with ECG or ECHO confirmation and who were on regular atorvastatin therapy 10 mg daily for more than one year who developed a cerebrovascular event in the form of ischemic stroke with CT or MRI Brain evidence within 5 years of occurrence of the first coronary event were included in the study.

Group 2 CONTROLS: A suitable control of 50 patients matching age, sex, smoking, alcohol and diabetes who had coronary artery disease and were also on atorvastatin therapy 10 mg for more than 5 years were included. These patients should have normal CT brain and no prior history suggestive of transient ischemic attacks.

Study size: 50

Study type: case control study

The age ranges from 40 to 80 and the study included both sexes. The study was approved by institutional ethics committee. The risk factors associated with, both modifiable like cigarette smoking, alcohol consumption, hypertension, diabetes mellitus and obesity (BMI) and non-modifiable like age, sex, family history was taken into consideration. The risk factors smoking and alcohol were found out by careful history taking. The risk factors DM and HT were detected by past medical history and laboratory routine investigation and BP measurement.

Total cholesterol HDL Cholesterol and triglycerides were measured in overnight fasting of 10 hrs. at 7 a.m. in

the morning using Hitachi 704 Analyser. Low density lipoprotein Cholesterol was calculated by the FRIEDWALD formula $LDL\text{-}chol = total\ chol - HDL\text{-}chol - Triglycerides/5$ which is internationally accepted. Non HDL cholesterol was calculated by deducting HDL from total cholesterol. Both cases & controls were established coronary artery disease with ECG and ECHO confirmation. All the basic blood investigations were done and their body mass index was calculated and the presence of metabolic syndrome was analysed. Those who had elevated renal parameters or abnormal liver function tests were excluded from the study.

RESULTS

Total cholesterol HDL Cholesterol and triglycerides were measured in overnight fasting of 10 hrs at 7 a.m in the morning using Hitachi 704 Analyzer. LDL Cholesterol was calculated by using the Freidwald's formula $LDL\ cholesterol = total\ chol - [High\ density\ lipoprotein\ cholesterol - Triglycerides/5]$ which is internationally accepted. Non HDL cholesterol was calculated by deducting HDL cholesterol from total cholesterol.

Table 1: Total Cholesterol

Total Chol	Cases	Controls
<200	29	39
200-239	19	11
>240	2	0
Total	50	50

58% of cases 78% of controls had their total cholesterol within optimal levels. The mean total cholesterol among cases was 197.14 mg/dl. The mean total cholesterol among controls was 180.34 mg/dl. The effect of statins on reducing the total cholesterol was evident.

Unpaired t test results

P value and statistical significance:

The two-tailed P value equals 0.0050. By conventional criteria, this difference is considered to be very statistically significant.

Confidence interval:

The mean of Group One minus Group Two equals 16.8000.

95% confidence interval of this difference: From 5.2030 to 28.3970

Intermediate values used in calculations:

$t = 2.8748$; $df = 98$. standard error of difference = 5.844

Table 2: HDL Cholesterol in Men

MEN HDL	Cases	Controls
≤ 20	1	0
21-40	22	13
41-50	5	11
51-60	1	4
>60	0	1
TOTAL	29	29

79.3% of cases and 44.8% of controls had $HDL < 40$ which is considered as a significant value for the development of atherosclerosis.

Table 3: HDL cholesterol in women

Women HDL	Cases	Control
<20	0	0
21-40	13	3
41-50	3	11
51-60	5	6
>60	0	1
Total	21	21

76.1 % of women cases and 66.6 % of controls had significantly low HDL cholesterol. The mean HDL cholesterol among (both men and women) cases was 37.6 mg/dl. The mean HDL cholesterol among controls was 44.4 mg/dl.

UNPAIRED T TEST RESULTS:

P value and statistical significance: The two-tailed P value is less than 0.0001. This difference is extremely statistically significant.

Confidence interval: The mean of Group One minus Group Two equals -6.6000

95% confidence interval of this difference: From -9.7602 to -3.4398

Intermediate values used in calculations: $t = 4.1445$; $df = 98$; standard error of difference = 1.592

Table 4: Triglycerides

TGL	Cases	Controls
<150	5	6
150-199	24	27
>199	21	17
Total	50	50

Only 10 % of cases and 12 % of controls had optimal triglyceride levels. The results indicate that statins did not help much in reducing triglycerides in the population studied. The mean triglycerides among cases were 194.4mg/dl. The mean triglycerides among controls was 190mg/dl

Unpaired t test results

P value and statistical significance: The two-tailed P value equals 0.5444. This difference is considered to be not statistically significant.

Confidence interval: The mean of Group One minus Group Two equals 3.5600. 95% confidence interval of this difference: From -8.0553 to 15.1753. Intermediate values used in calculations: $t = 0.6082$; $df = 98$; standard error of difference = 5.853.

Table 5: Triglycerides statistics

Group	Cases	Controls
Mean	193.1600	189.6000
SD	30.5700	27.9000
SEM	4.3233	3.9457
N	50	50

The average VLDL among cases was 38.8mg/dl. The average VLDL among controls was 30mg/dl. Since VLDL was calculated from triglycerides test of significance was not applied.

Table 6: Trends in LDL

LDL	Cases	Controls
<70	0	2
70-99	11	23
100-129	19	22
130-159	18	3
160-189	2	0
190 and above	0	0
Total	50	50

22% of cases and 46% of controls had their LDL cholesterol within optimal results. Only 4 % of controls had reached the target LDL value. Since both cases and controls were on regular atorvastatin therapy levels the LDL levels of many patients were near optimal levels. The mean LDL cholesterol among cases was 121.34 mg/dl. The average LDL Cholesterol among controls was 98.72 mg/dl.

P value and statistical significance: The two-tailed P value is less than 0.0001: This is considered to be extremely statistically significant.

Confidence interval: The mean of Group One minus Group Two equals 22.6200. 95% confidence interval of this difference: From 12.5598 to 32.6802. Intermediate values used in calculations: $t = 4.4620$; $df = 98$; standard error of difference = 5.069.

Table 7: The non HDL Cholesterol

NON HDL	Cases	Controls
<100	0	2
100-129	10	17
130-159	14	27
160-199	24	4
200 and above	2	0
Total	50	50

The cut off for non HDL cholesterol is generally thirty mg/dl more than LDL cut off values. 38 % of controls had their non-high density lipoprotein cholesterol in the optimal range. But only 20 % of cases had their non HDL cholesterol in the optimal range. The mean non HDL cholesterol among cases is 160.04 mg/dl. The mean HDL cholesterol among controls is 136.64 mg/dl.

Unpaired t test results

P value and statistical significance: The two-tailed P value is less than 0.0001: By conventional criteria, this difference is considered to be extremely statistically significant. The mean of cases minus controls equals 23.4. 95% confidence interval of this difference: From 13.5500 to 33.2500. Intermediate values used in calculations:

$t = 4.7144$; $df = 98$; standard error of difference = 4.964 d t test results. This indicates that the difference in non HDL cholesterol contributed significantly in the occurrence of a second ischemic event in the form of cerebrovascular accident in the study population. Despite statin therapy the difference in non HDL cholesterol remains a significant contributing factor in the development of cerebrovascular accident.

DISCUSSION

Our study population had significantly low HDL, high Non HDL, high LDL values, high total cholesterol values and high BMI compared to controls. The Triglyceride matched the control population. The importance of non HDL cholesterol is stressed on patients with high triglycerides in various literatures. In our population though the triglycerides were not significantly elevated the non HDL cholesterol values were still significantly high. So it stresses the importance of routinely looking beyond LDL cholesterol in all patients. Non HDL cholesterol was not superior to LDL cholesterol but was equally significant. Statins as a class reduce LDL cholesterol. They also reduce total cholesterol & triglycerides to a certain extent. But their effect on HDL cholesterol is not uniform. Atorvastatin has got no role in reducing non HDL cholesterol values. Only newer drugs with high potency including rosuvastatin and simvastatin elevate HDL Cholesterol and reduce non HDL cholesterol. The importance of non HDL cholesterol is well established in patients with elevated triglycerides and diabetes population. Our study stresses the importance of routinely focussing on non HDL Cholesterol as a parameter as it is more accurate as it's got by deducting total cholesterol from HDL cholesterol both of which are directly measured. Majority of labs report calculated LDL value using Friedwalds equation and it does not give us the clinically important atherogenic LDL particle level. LDL level is a predicted value. In our study patients on atorvastatin therapy were chosen as we wanted to stress the importance of non HDL Cholesterol values on patients with LDL cholesterol values that were likely to be lower than the general population as they were on atorvastatin therapy. However since it was a case control study the dose of atorvastatin was not titrated to meet the target LDL values and the desired results could not be obtained. But still our study clearly establishes the definitive role of non HDL cholesterol on par with LDL cholesterol in assessing the risk of ischemic stroke. Drugs that reduce non HDL cholesterol include rosuvastatin, simvastatin, niacin and fibrates. However life style modifications are the most effective treatment strategy. In our study the average total cholesterol value among cases was 197.14.

The average of the total cholesterol value among controls was found to be 180.34. The p value was found to be $p = 0.0050$ which was found to be statistically significant. The low values were due to the use of statins. This is in concordance with the study conducted on total cholesterol⁶ by various studies and Cleveland heart society and ATP 3 guidelines.⁷ In our study the average LDL cholesterol value among cases was 121.34 mg/dl. The average of the LDL cholesterol value among controls was found to be 98.72 mg/dl. Though this was low when compared to patients who developed CAD but who were not on STATIN therapy (which is 135-140mg/dl)^{8,9}, only 4% of the total 50 % cases and 50% controls had attained the target LDL which is set at 70mg/dl. The p value was found to be $p < 0.0001$ which was found to be statistically significant. The relatively low values were due to the use of statins. In our study the average triglyceride value among cases was 193.16. The average of the triglycerides value among controls was found to be 189.6. The p value was found to be 0.544 which was not found to be statistically significant. The low values were due to the use of statins. In the analysis by miler *et al* the average triglyceride value was 200.3 on patients on statin therapy.¹⁰ In our study the average HDL cholesterol value among cases was 37.1 mg/dl. The average of the HDL cholesterol value among controls was found to be 43.7. The p value was found to be $p < 0.0001$ which was found to be statistically significant. This is in concordance with the study conducted on HDL cholesterol by chapman *et al* where the average HDL cholesterol was 36.84 for patients on statin therapy.¹¹ In our study the average non HDL cholesterol value among cases was 160.04mg/dl. The average of the Non HDL cholesterol value among controls was found to be 136.64 mg/dl. The p value was found to be $p < 0.0001$ which was found to be statistically significant. Though the control group had low values of non HDL cholesterol it was not within the target range set by ATP 3 guidelines which is set at 100 mg/dl. This is in concordance with the study conducted by Susan *et al* where the average non HDL cholesterol for patients on statin therapy was 137.2. This matches our control population.⁶

CONCLUSION

The results of the study were that the mean non HDL Cholesterol was 198.8 mg/dl. The mean non HDL cholesterol of controls was 129.42mg/dl. In this study and other similar studies the control population was not CAD patients on statin therapy. Hence exact comparison

could not be made out. This indicates that the difference in non HDL cholesterol contributed significantly in the occurrence of a second ischemic event in the form of cerebrovascular accident in the study population.

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