Non Hdl Cholesterol As A Risk Factor for Ischemic Stroke in Patients With Coronary Artery Disease on Statin Therapy

DR. K.NAMASIVAYAM	DR. P.V.KRISHNAN	DR.N.K.SENTHILNATHAN
M.D, ASSOCIATE PROFESSOR OF MEDICINE, K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE, TIRUCHIRAPALLI, TAMILNADU.	M.D, ASSOCIATE PROFESSOR OF MEDICINE K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE, TIRUCHIRAPALLI, TAMILNADU.	M.D, ASSOCIATE PROFESSOR OF MEDICINE K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE, TIRUCHIRAPALLI, TAMILNADU.

* DR.L.MUTHUMANI	DR.ALEN BINNY
M.D, ASSISTANT PROFESSOR OF MEDICINE K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE, TIRUCHIRAPALLI, TAMILNADU. * CORRESPONDING AUTHOR	JUNIOR RESIDENT IN MEDICINE K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE, TIRUCHIRAPALLI, TAMILNADU.

ABSTRACT *Patients on statin therapy have relatively low LDL cholesterol but still a significant number of patients develop a second coronary or cerebrovascular events. The study was conducted to stress the importance of other parameters of lipid profile in bringing down the ischemic events. Both cases & control were established coronary artery disease with ECG and ECHO confirmation. In our study LDL cholesterol, HDL cholesterol and non HDL cholesterol had equal "p" values in predicting risk of ischemic strokes. In spite of risk reduction with reduction of LDL cholesterol levels, in certain subgroup of patients the risk of atherosclerotic events remains high. Non HDL cholesterol has a significant contribution to risk assessment and goal monitoring in ischemic stroke patients.*

INTRODUCTION

The role of LDL cholesterol in predicting the risk of coronary and cerebrovascular events has been well established. But other particles that contain Apo protein B such as VLDL, VLDL remnants, IDL, and chylomicron remnants are important [1]. This is reflected in the non HDL cholesterol value which is a simple measure. Patients on statin therapy have relatively low LDL cholesterol but still a significant number of patients develop a second Coronary or Cerebrovascular events. In those patients other parameters in lipid profile such as triglycerides, low HDL cholesterol, & lipoprotein A and other remnant lipoprotein are important. The study was conducted to stress the importance of other parameters of lipid profile in bringing down the ischemic events.

AIM

The aim is to study whether non HDL cholesterol has got significant role in assessing the risk of ischemic stroke in established coronary artery disease patients who were on atorvastatin therapy.

MATERIALS AND METHODS

This study was done in Mahatma Gandhi Memorial Government hospital attached to K.A.P .Govt. Medical College, Tiruchirapalli during the period from May 2013 to December 2015

INCLUSION CRITERIA

Patients on established coronary artery disease who were on Atorvastatin therapy 10 mg for more than 1 year , who developed an ischemic stroke evidenced by CT scan or MRI within 5years of occurrence of the first coronary events.

EXCLUSION CRITERIA

Age less than 40years
Patients on irregular statin therapy
Patients with chronic kidney disease
Patients with chronic liver disease
Patients who had poor left ventricle function

STUDY DESIGN

Number of study groups   : TWO

Group 1 CASES: 50 patients with a history of coronary artery disease with ECG or ECHO conformation and who were on regular Atorvastatin therapy 10mg daily for more than one year who developed a cerebrovascular events in the form of ischemic stroke with CT or MRI brain evidence within 5years 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 10mg for more than 5year were included. These patients should have normal CT brain and no prior history suggestive of transient ischemic attacks.

SAMPLE SIZE: 50
STUDY TYPE: Case-Control study
The age ranges from 40 to 80 and the study included both sexes. 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 Diabetes and Hypertension were detected by past medical history and laboratory investigation and BP measurement.

Total cholesterol HDL, Cholesterol and triglycerides were

measured in overnight fasting 10hrs, at 7am in the morning using Hitachi 704 analyzer. Low density lipoprotein cholesterol was calculated by the FRIED WALD formula LDL cholesterol = total cholesterol - HDL cholesterol-Triglycerides/5 which is internationally accepted. Non HDL cholesterol was calculated by deducting HDL from total cholesterol. Both cases & control had established coronary artery disease with ECG and ECHO confirmation.

All the basic blood investigations were done and their body mass index was calculated.

Descriptive statistics were used to calculate the frequency, mean, median, and standard deviation.

RESULTS

In our study the mean age of the population was 66.4 years. The majority of patients in our study were in the age group 60 to 69 years.The age sex ratio indicates that females had later onset of vascular events compared to males.

There were 29 males & 21 females. Their average age was 67.72 years; females were somewhat elder to their male counterparts. Most of them belonged to the 60-69 years age group (50%).

Out of the 50 patients 20 were smokers which accounts to 40%. All the 21 females were nonsmokers. But 17 of the females were exposed to passive smoking.Out of the 50patients 20 were alcoholics which accounts to 40% out of the 21 females one was an alcoholic. The controls were matched for smoking and alcoholic. Except that the lone female alcoholic could not be suitable matched.

Out of the 50 patients studied 16 were known diabetes patients on treatment accounting to 32% of cases.The controls were matched for diabetes.

Out of the 50 patients 36% were hypertensive. The control were matched for hypertension.

BODY MASS INDEX

88% of cases and 80% of control were having a higher than normal BMI. The results showed that with increasing obesity the prevalence of multiple ischemic events was increasing. An increase in BMI with increasing age was observed. The average BMI among cases was 27.03, SD was 3.42 andaverage among control was 25.4,SD was 2.97. The P value was 0.0125 which was statistically significant. There was high prevalence of sedentary life style and faulty eating habits. Since both the cases and controls were on atorvastatin therapy they had the wide spread belief that they can adopt these faulty habits. Proper counseling was given to all the 100 patients included in the study.

WAIST HIP RATIO

66.6% of women and 75.8% of men were having a higher than normal waist circumference.

SERUM LIPID PROFILE

Total cholesterol HDL cholesterol and triglycerides were measured after overnight fasting of 10hrs at 7am in the morning using Hitachi 7.4 analyzer.LDL cholesterol was calculated by using the FREIDWALD's formula LDL cholesterol = total cholesterol - 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	Cases	Control
<200	29	39
200-239	19	11
>240	2	0
Total	50	50

58% of cases 78% of control 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 180.34mg/dl. The effect of statins on reducing the total cholesterol was evident.The two – tailed P value equal 0.0050. By conventional criteria, this difference is considered to be statically significant.

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

HDL in WOMEN	Cases	Controls
<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 37.6mg/dl. The mean HDL cholesterol among control was 44.4 mg/dl.

The two – tailed p value is less than 0.0001.This difference is statistically significant.

Table: 4 TRENDS IN 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 triglycerides levels, the results indicate that statins did not help much in reducing triglycerides in the population studied.

The mean triglycerides among cases were 194.4% mg/dl. The mean triglycerides among controls was 190mg/dl. The two – tailed p value equals 0.5444.This difference is statistically not significant.

TRENDS IN VLDL

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: 5 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, 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. The two-tailed P value is less than 0.0001. This is considered to be statistically significant.

NON HDL CHOLESTEROL

The cut off for non HDL Cholesterol is generally 30 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% cases had their non HDL cholesterol in the optimal range. The mean non HDL cholesterol among cases is 160.64 mg/dl. The mean HDL cholesterol among controls is 136.64mg/dl.

The two tailed p value is less than 0.0001: This is statistically significant.

DISCUSSION

LDL cholesterol is widely recognized as the marker of coronary artery disease. Stains have good effect in lowering LDL cholesterol value. But still patients develop ischemic events. So the importance of looking beyond LDL cholesterol arises. Further non HDL cholesterol is a calculated value using total cholesterol and HDL both of which are got from direct measurements whereas LDL cholesterol is a predicted value using FRIEDWALDS equation in most of the labs in India like our lab. Non HDL cholesterol includes all the atherogenic particles in the lipid profile. Hence it's considered to have a superior predictive value. Atorvastatin is one of the most commonly prescribed lipid lowering drug in our hospital. Its beneficial effects include lowering LDL, and triglycerides to a certain extent. It does not cause significant increase in HDL like that Rosuvastatin. Hence it has little effect in altering the non HDL cholesterol value. So the aim was to study if Non HDL cholesterol got significant role in assessing CVA risk in a population with relatively low LDL levels

Total cholesterol

The average total cholesterol values among case 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=0.005 which was found to be statistically significant.

This is in concordance with the study conducted on total cholesterol by various studies and Cleveland heart society and ATP 3 guidelines [2].

LDL Cholesterol

The average LDL cholesterol in cases was 121.34mg/dl and in controls was 98.72mg/dl. The p value was found to be <0.0001 which is significant.

Triglycerides

The average triglyceride value among cases was 193.16. The average of the triglyceride 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 in patients on statin therapy[3].

HDL Cholesterol

The average HDL cholesterol value among cases was 37.1mg/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 patient on statin therapy[4].

Non HDL cholesterol

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 136.64mg/dl. The p value was found to be p<0.0001 which was found to be statistically significant. Though the control group had low value of non HDL cholesterol it was not within the target range set by ATP 3 guidelines which is set at 100mg/dl. This is in concordance with the study conducted by Susan et al where the average on HDL cholesterol for patients on statin therapy was 137.2[5]. This matches our control population.

Pravin et al[6] conducted a study to stress the importance of non HDL cholesterol on ischemic stroke patients. The results of the study were that the mean non HDL cholesterol was 198.8mg/dl. The mean non HDL cholesterol on control was 129.42mg/dl. In this study and other similar studies the control population was not Coronary Artery Disease 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.

CONCLUSION

In our study LDL cholesterol, HDL cholesterol and non HDL cholesterol had equal 'p' values in predicting risk of ischemic strokes. In spite of risk reduction with reduction of LDL cholesterol levels in certain sub group of patients the risk of atherosclerotic events remains high. Other factors like triglycerides, non HDL cholesterol, Apo lipoproteins, lipoprotein A and are important. Non HDL cholesterol has a significant contribution risk assessment and goal monitoring in ischemic stroke patients. Since LDL reported by most of the labs is a calculated and predicted value they should be routinely encouraged to report the non HDL cholesterol values which is more accurate and physicians should routinely target non HDL cholesterol for treatment.

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