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Variation of Carotid Intima - Media Thickness in Hypercholesterolemia Patients on Atorvastatin and Rosuvastatin Therapy

Samia Perwaiz Khan[1]*, Pashmina Gul[2], Khwaja Zafar Ahmed[3], Rubina Ghani[4] and Zia Yaqub[5]

[1]*Associate Professor, Pharmacology, Ziauddin University, Karachi, Pakistan*
[2]*Dr. Ziauddin Hospital, Karachi, Pakistan*
[3]*Department of Radiology, Ziauddin College of Pharmacy, Ziauddin University, Karachi, Pakistan*
[4]*Assistant Professor, Baqai Medical University, Karachi, Pakistan*
[5]*Consultant Cardiologist, National Institute of Cardiovascular Diseases, Karachi, Pakistan*

Abstract

Aims of study: This study compares changes in lipid profile and carotid intima-media thickness and their use as surrogate biomarkers, after treatment with atorvastatin and rosuvastatin given to hypercholesterolemia patients.

Methodology: Lipid profile was done after overnight fasting in patients with history of hypercholesterolemia or family history of premature coronary artery diseases. B-mode ultrasonography was done to measure mean carotid intima-media thickness on a Toshiba (M# SSA-580A/E2) ultrasound scanner with linear probe. Both treatment groups, one on atorvastatin (20 mg) and other on rosuvastatin (10 mg) were followed-up for two years.

Results: Total of forty two patients of heterozygous familial hypercholesterolemia were followed -up for two years. Total cholesterol reduction was (45%) and LDL-cholesterol (48%) in patients on rosuvastatin 10 mg/day, as compared to total cholesterol reduction (36%) and LDL-cholesterol (37%) in patients on atorvastatin 20 mg/day (**$p < 0.001$). The mean CIMT regression in both treatment groups was significant (0.11 mm) in rosuvastatin treatment group and (0.08 mm) in atorvastatin treatment group (*$p < 0.02$).

Conclusion: This study has shown better efficacy of rosuvastatin as compared to atorvastatin in reduction of LDL-cholesterol and carotid – intima media thickness.

Keywords: CIMT; Atherosclerosis; HMG-CoA reductase inhibitor; LDL-cholesterol; Atorvastatin; Rosuvastatin; Heterozygous familial hypercholesterolemia (HeFH)

Introduction

Atherosclerosis is a disease of the arteries in which fatty material and plaque are deposited in the arterial wall, resulting in narrowing of the lumen and eventual impairment of blood flow. The development of atherosclerosis may occur when deposits of cholesterol and plaque accumulate at a tear in the inner lining of an artery. As the deposits harden and occlude the arterial lumen, blood flow to distant tissues decreases and a clot may become lodged in the artery thus completely blocking it [1,2].

High cholesterol and other lipid disorders can be inherited or associated with secondary causes. Heterozygous familial hypercholesterolemia (HeFH) is a monogenic disorder that affects about 1 in 500 people, with a higher prevalence in certain subpopulations such as people of Quebec [3]. Lebanese [4] and Afrikaners [5]. HeFH is characterized by cholesterol deposits affecting the corneas, eyelids and extensor tendons. Elevated plasma concentrations of low-density lipoprotein cholesterol (LDL-C) and premature coronary artery diseases are associated symptoms. HeFH is caused by mutations in the low density lipoprotein receptor gene encoding the LDL receptor.

The drugs used in treatment of hypercholesterolemia include statins. They decrease synthesis of cholesterol in the liver by inhibiting HMG COA reductase, a key enzyme in cholesterol synthesis and reduce LDL-cholesterol. The hepatocytes decrease production of very low density lipoproteins (VLDL), increase activity of LDL receptors. They reduce LDL cholesterol by 30% to 55%. They also have anti-inflammatory effect by decreasing intra-arterial and systemic inflammation through enhanced production of endothelial nitric oxide and decreasing LDL deposition in endothelial macrophages and cholesterol in inflammatory cells [6].

B-mode ultrasound is a non-invasive technique used to measure atherosclerosis in superficial arteries. It is a measure of carotid walls intima-media thickness. Increase in thickness is associated with an increased risk of coronary artery diseases [7].

B-mode ultrasound is a relatively simple, safe, inexpensive and reproducible measure used in clinical research. This technique is useful in evaluating new risk factors and the progress of arterial wall thickness. By comparing with the normal value of CIMT we can determine the relationship of altered CIMT with atherosclerosis risk factors. Measurement of carotid intima-media thickness is used for determining atherosclerosis and prevents consequences such as coronary artery diseases and stroke. It is a noninvasive marker for measurement of arterial wall thickness and stiffness [8]. The statins not only reduce the LDL-cholesterol and total cholesterol by inhibiting 3-hydroxy-3-methyglutaryl Co-enzyme A but also have anti-inflammatory action and improve the endothelial functions [9,10].

***Corresponding author:** Samia Perwaiz Khan, Associate Professor Pharmacology, Ziauddin University, 4/B, Shahrah Ghalib, Block, 6 Clifton, Karachi 75600, Pakistan, Tel: 00 92 21 35862939; Fax: 00 92 21 35862940; E-mail: samiaperwaiz@hotmail.com

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Improvement in endothelial function results in reduction of carotid intima-media progression.

A number of studies have shown strong association between carotid intima-media thickness and myocardial infarction and stroke [11,12].

Hypothesis

High LDL- C and progression in carotid intima – media thicknesses are risk factors for atherosclerosis. Our aim was to compare the effectiveness of statins, rosuvastatin and atorvastatin in lowering LDL-C and decrease in carotid intima-media thickness.

To our knowledge no similar direct comparison study has been done to assess the effectiveness of rosuvastatin to atorvastatin in the treatment of hypercholesterolemia patients by measuring carotid intima-media thickness.

Study design

Hypercholesterolemia patients having premature coronary artery diseases, family history of cardiac diseases or hyperlipidemia were selected from National Institute of Cardiovascular Diseases and Dr. Ziauddin Hospital. Duration of this clinical trial was from June 2008 to June 2010 (2 years duration). Out of total hypercholesterolemia patients who participated in this study six were already on statin therapy due to premature coronary artery diseases.

This study was approved by the ethics committee of Ziauddin University. All patients who participated in the study gave written consent. Also written consent of all the controls was taken. Out of the total, forty two hypercholesterolemia patients who participated in the follow-up study were divided into two groups of twenty one cases on atorvastatin (20 mg) and twenty one cases on rosuvastatin (10 mg), lipid profile and measurement of carotid intima media thickness repeated after two years therapy.

We also measured the carotid intima media thickness of twenty controls with normal lipid profiles.

Inclusion criteria: All those patients with total cholesterol greater than 200 mg/dl and LDL-cholesterol greater than 160 mg/dl were included in this study. The patients were also assessed for positive family history of early coronary heart diseases, tendon xanthomas, xanthelasmas, arcus cornealis and early onset of coronary heart diseases (acute coronary syndrome, myocardial infarction) and cerebrovascular diseases.

Exclusion criteria: All those hyperlipidemic patients were excluded having diabetes mellitus, hypertension, history of smoking, thyroid or any drug history of corticosteroids, thiazides, protease inhibitors.

Methodology

Participants

Two hundred and forty lipid profiles were done of which one hundred and twenty were found to have hypercholesterolemia. The cases who participated in this study were with history of premature coronary artery diseases or family history of hyperlipidemia and coronary artery diseases. Their age range was between (26 to 60 years). Forty two of these patients agreed to participate in this clinical trial after being diagnosed as cases of hypercholesterolemia all having family history of premature coronary artery diseases. Baseline characteristics of 42 patients assigned to either atorvastatin or rosuvastatin treatment groups were noted.

Lipid profile

Blood samples were collected for lipid profiles after overnight fasting of twelve hours. Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were determined by autoanalyser, by using Hitachi Kits. Lipid profiles were done initially and after 6, 12 and 24 months of therapy.

Measurement of Carotid intima- media thickness

The investigation of measurement of carotid intima- media thickness by B-mode ultrasound, was conducted in the radiology department of Dr. Ziauddin Hospital. B-mode ultrasound of carotid intima-media thickness measurement, of common carotid, carotid bifurcation and internal carotid of left and right carotid arteries were performed with linear probe of Toshiba (M# SSA-580A/E2) ultrasound scanner. The distance between the leading edge first bright line of far wall (lumen intima interface) and the leading edge of the second bright line (media-adventitia interface) measured as intima- media thickness [13-17]. The average mean of six segments of intima media thickness was taken as mean CIMT. Assessment of CIMT at multiple sites determined frequent plaque and increase thickening that were more common at carotid bifurcation [18] in patients with raised LDL-cholesterol. Plaques were observed mostly at bifurcation in eleven of the forty two cases of hypercholesterolemia and of these twenty one had developed premature coronary artery diseases.

This study was done to determine the effect on lipid profile and carotid intima-media thickness by therapy of low dose statins for duration of twenty four months. The baseline and after two years carotid intima-media thickness were measured in patients with hypercholesterolemia.

Statistical Analysis

Data was presented as mean and standard deviation for continuous variables. SPSS software (version 16.0) was used for statistical analysis. Correlation of mean carotid intima-media thickness and total cholesterol, CIMT and LDL-cholesterol were determined by Pearson's correlation in hypercholesterolemia cases.

Difference in baseline mean values and after twenty four months hypolipidemic therapy was assessed by using Students t- test, to compare the means of total cholesterol, LDL-cholesterol, HDL-cholesterol and regression in CIMT before and after treatment with atorvastatin (20 mg) and rosuvastatin (10 mg). $P<0.05$ was considered statistically significant. This study was done to determine the effect on lipid profile and carotid intima-media thickness by statin therapy.

Results

One hundred and twenty patients of heterozygous hypercholesterolemia were diagnosed after performing two hundred and forty lipid profiles. All those subjects with diabetes, hypertension, thyroid diseases and on drug causing hyperlipidemia were excluded. They were from all provinces of Pakistan as well as immigrant population living in Karachi. Age range was between 26 to 60 years.

Baseline characteristics of hypercholesterolemia patients on atorvastatin and rosuvastatin therapy

Forty two cases participated in clinical trial. All these were hypercholesterolemia had total cholesterol >200 mg/dL and LDL > 160 mg/dL and all had a positive family history of premature coronary artery diseases. Eleven of these had plaques at various sites of their

carotid arteries, while eleven of these patients had xanthomas and arcus cornealis and twenty one patients had premature coronary artery diseases.

They were grouped into twenty one on atorvastatin (20 mg) and another group of twenty one on rosuvastatin (10 mg) and their baseline lipid profile and carotid intima-media thickness were compared to changes in lipid profile and carotid intima media thickness after 24 months therapy (Figure 1).

Correlation of total cholesterol and LDL-Cholesterol with CIMT

CIMT of hypercholesterolemia patients was measured as shown in (Figure 2A) and plaque is seen in (Figure 2B). By applying Pearson's correlation a positive correlation was observed between carotid intima media thickness with total cholesterol ($r = 0.638^{**}$, $p<0.01$) and carotid intima- media thickness with LDL–cholesterol($r= 0.725^{**}$, $p<0.01$) in cases of familial hypercholesterolemia.

Effects of rosuvastatin and atorvastatin on lipoprotein levels

The patients on hypolipidemic therapy of atorvastatin had a percentage reduction of total cholesterol 36% and LDL-cholesterol 37%. In rosuvastatin group there was more significant reduction of total cholesterol 45% and LDL-cholesterol 48%, ($p< 0.001$). Increase in HDL- cholesterol was not significant in rosuvastatin or atorvastatin group. Comparing both treatments, rosuvastatin had more significant effect in reducing total cholesterol and LDL-cholesterol as compared to atorvastatin therapy (Table 1a and 1b).

Effects of rosuvstatin and atorvastatin on CIMT

The regression in the carotid intima –media thickness was 0.08 mm for atorvastatin while it was 0.11 mm for rosuvastatin. The CIMT regression with rosuvastatin therapy was statistically significant at $p<0.02$ and percentage changes from baseline are given (Table 2).

Side effects in two treatment groups

Although the levels of LDL- cholesterol in familial hypercholesterolemia patients were reduced significantly, the levels of alanine amino transferase were raised in one patient on rosuvastatin therapy.

Discussion

The study has shown that there was significant reduction of total cholesterol and LDL-cholesterol, triglycerides and regression of carotid intima-media thickness in patients with heterozygous familial hypercholesterolemia after statin treatment. A direct comparison of rosuvastatin and atorvastatin has shown rosuvastatin to be more potent in reducing total cholesterol and LDL-cholesterol. Since there is direct correlation in LDL-cholesterol and carotid intima-media reduction, this may be the possible explanation for rosuvastatin having more significant effect in reducing carotid intima-media thickness as it is more effective in reducing LDL-cholesterol levels.

Increased levels of LDL-cholesterol in patients with heterozygous familial hypercholesterolemia have shown a positive correlation to progress in carotid intima-media thickness [19]. There is a moderate correlation in increase in LDL-cholesterol to CIMT in our study.

Statins prevent stroke and there was seen a correlation in LDL-cholesterol and progression of CIMT [20]. In study done by Smlide et al. atorvastatin group showed regression in carotid- intima media thickess, Simvastatin group showed progression in carotid- intima

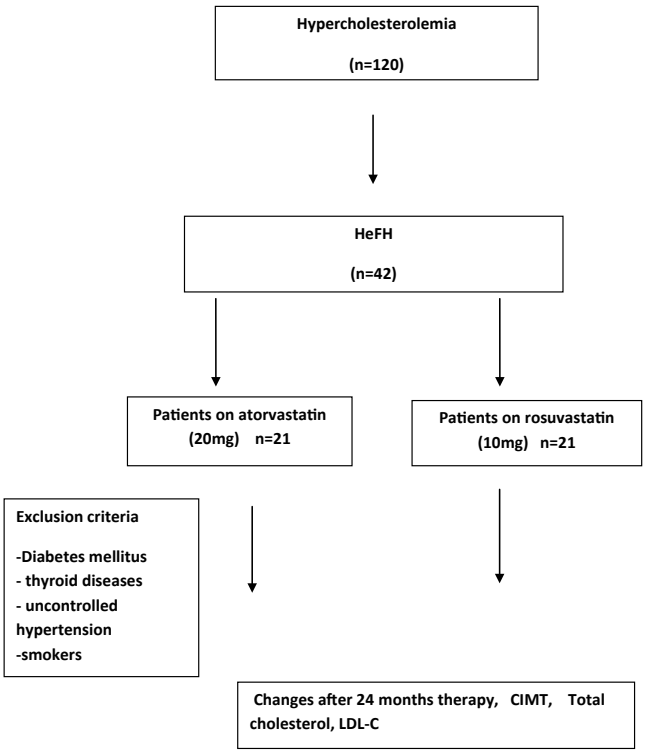

Figure 1: Entry of patients in study and follow-up of cases.

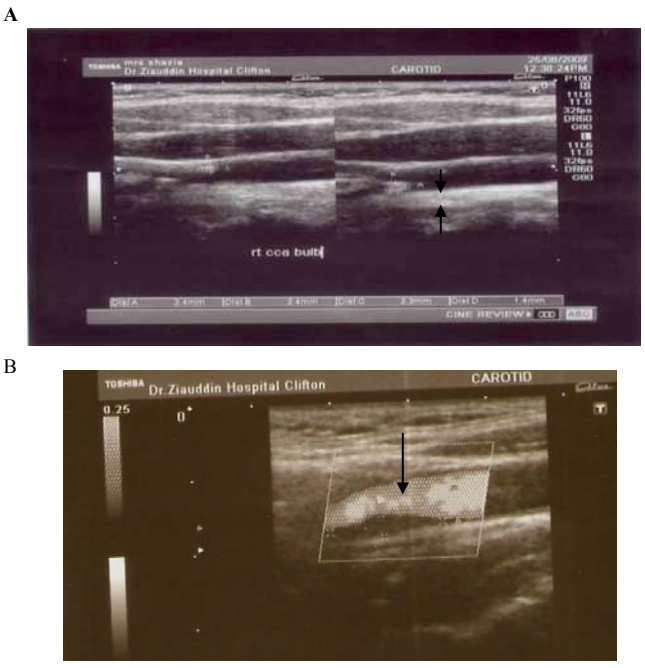

Figure 2: B-mode ultrasound show increased carotid intima- media thickness (2.4mm) along with plaques. B mode ultrasound of right carotid in patient with severe hypercholesterolemia, plaque at right bulb measuring 3.0 x 14.5 mm.

Atorvastatin (20mg/day) N= 21					
Variables	**Baseline Mean (SD)**	**After 2 years Treatment Mean (SD)**	**Changes**	**Change (%)**	***p**
Total cholesterol(mg/dL)	247 ± 40	157 ± 51	- 90	36	0.001***
LDL- C(mg/dL)	182 ± 25	115 ± 65.7	-67	37	0.001***
Triglycerides (mg/dL)	211. 5 ± 70	183 ±100	-28	13	0.001***
HDL-C (mg/dL)	31.57 ± 9	42 ±11.5	+ 8	19	0.001***
CIMT mean(mm)	0.80 ±0.24	0.72 ± 0.22	-0.08	10	0.001***

Decrease in lipoprotein levels from baseline CIMT after 2 years atorvastatin therapy. Ranges of total cholesterol reduced 36-50%, LDL-C reduced 37-60%

Table 1a: Changes from Baseline in Lipid profile and CIMT after 2 years Atorvastatin Therapy.

Rosuvastatin (10mg/day) N=21					
Variables	**Baseline Mean (SD)**	**After 2 years Treatment Mean (SD)**	**Changes**	**Change (%)**	**p**
Total cholesterol(mg/dL)	271 ± 70	148 ± 48	-123	45	0.001***
LDL-cholesterol (mg/dL)	202 ± 62	202 ± 62	- 97	48	0.001***
Triglycerides (mg/dL)	198 ± 90	126 ± 65	- 72	36	0.001***
HDL-cholesterol(mg/dL	39 ±13	49 ±14	+ 10	20	0.001***
CIMT mean (mm)	0.78 ± 0.09	0.67 ±0.11	- 0.11	14	0.001***

Decrease in lipoprotein levels from baseline CIMT after 2 years Rosuvastatin therapy. Ranges of total cholesterol reduced 45-55% and LDL-C reduced 48-65%

Table 1b: Changes from Baseline in Lipid profile and CIMT after 2 years Rosuvastatin Therapy.

Variables	**Atrovastatin (20mg) (n=21) Change %**	**Rosuvastatin (10 mg) (n=21) Change %**	**P**
Total Cholesterol (%)	-36	-45	0.001***
LDL- Cholesterol (%)	-37	-48	0.001***
Triglycerides (%)	-13	-36	0.001***
HDL- Cholesterol (%)	+19	+20	0.391
CIMT mean (%)	-10	-14	0.02**

Table 2: Comparison of Percentage Changes in Atorvastatin and Rosuvastatin groups.

media thickness over 2 years therapy [21]. Increased progression of CIMT in early childhood is also treated with statins [22].

Our baseline mean carotid intima-media thickness of familial hypercholesterolemia was similar to that observed by de Groot et al. [13]. In their study the mean of carotid intima-media thickness in patients with familial hypercholesterolemia was (0.79 ± 0.20mm) as compared to controls where mean carotid intima-media thickness was (0.63 ± .014 mm) which is quite similar to the mean carotid intima-media thickness in our population. This study shows increased carotid intima-media thickness in cases of hypercholesterolemia and most of these patients have shown to have developed early coronary and cerebrovascular diseases. There was correlation between increase in carotid intima-media thickness and LDL-cholesterol. In eleven patients with familial hypercholesterolemia several arterial plaques were seen. Number of these plaques reduced in size after two years of rosuvastatin therapy.

In another study done on patients on hypolipidemic therapy for twenty nine months mean CIMT was reduced from 0.83 mm to 0.68 mm [23]. In this study reduction in mean CIMT in atorvastatin group was reduced from 0.8mm to 0.72mm and in the rosuvastatin group from 0.78 mm to 0.67 mm. Study done by Taylor et al. [6] has shown that atorvastatin had significant effect of reduction of carotid intima-media thickness compared to pravastatin.

The measures of common carotid are taken as valid surrogate marker for progression of atherosclerosis. In order to find the applicability and use in prevention and therapy it can be a standardized protocol for both observational studies and applied clinical research. CIMT should be measured preferably on the far wall values as the near walls are less reliable. It is possible to visualize plaques in the artery with ultrasound technique. Plaque is a focal structure encroaching into the arterial lumen [24].

Bifurcation was found to have highest correlation with CIMT. If single ultrasound is to be used, bifurcation should be the preferred site [18]. In this study it was seen that an increase in mean thickness was more in the area of bifurcation. Also calcified plaques were seen in patients with very high LDL-cholesterol levels. Study by Agewall et al. [24] compared the carotid intima-media thickness to the clinical outcome during 6 years follow-up in high risk population.

Study by Crouse et al. [25] determined significant reduction of carotid intima- media thickness in individuals with subclinical atherosclerosis after two years rosuvastatin therapy.

In this study of forty two patients with hypercholesterolemia who were followed up for CIMT and lipid profile, significant reduction of total cholesterol, LDL-cholesterol and carotid intima- media thickness was seen after atorvastatin and rosuvastatin therapy. The size of plaque was observed to be reduced after atorvastatin and rosuvastatin therapy, soft plaque had regressed completely in two cases after two years follow-up.

In this study heterozygous hypercholesterolemia patients on rosuvastatin have relatively greater reduction of LDL-cholesterol levels and significant regression of CIMT as compared to atorvastatin group.

Conclusion

This study has shown increase in carotid intima- media thickness in patients with hypercholesterolemia. Intervention by rosuvastatin has shown better efficacy in treatment although atorvastatin is also effective in reducing total cholesterol, LDL-cholesterol and reduces carotid intima-media thickness. B-mode carotid intima-media thickness measure is an inexpensive and convenient endpoint for the intervention therapy.

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