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Research article

EFFECT OF HMG Co-A REDUCTASE INHIBITORS ON ARTERIAL WALL THICKNESS IN HYPERTENSIVE SUBJECTS UNDERGOING LONG TERM TREATMENT.

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ABSTRACT

Background: Cholesterol lowering drugs are very widely used among patients with hypertension in order to prevent atherosclerosis and death. However several other changes are produced in such patients as a result of inhibition of cholesterol synthesis. Therefore in this preliminary study we evaluated the intima/media thickness in hypertensive subjects.

Material and methods: Cross section study in 20 hypertensive subjects on statins for more than an year and 20 hypertensives who were not on statins were studied. Twenty normal non hypertensive individuals were control subjects.Their Common carotid artery (CCA) was ultrasonologically examined and the Intima – Media thickness were determined.

Results: The Intima - Media thickness in Hypertensive subjects were significantly higher than those of control groupand also those hypertensive patients who were administered with statins ($p<0.001$). There was no statistically significant difference among the controls and statin administered patients. Further there was no gender difference in the results.

Conclusion: Hypertensive subjects who were on statin for more than an year have significantly reduced arterial wall thickness. Undesirable side effects of such thinning of vessel wall, which might result in aneurysmal dilatations, should be kept in mind especially while treating elderly hypertensive with HMG CoA reductase inhibitors.

Key Words: HMG CoA reductase inhibitors, hypertensive patients, carotid artery thickness.

INTRODUCTION

Hypertension is one of the most important causes of death among the population.[Roger VL, et al., 2012] However the death rate does not seem to abate even after the advent of a series of newer and potent medications available.[Ford ES, 2011]. Atherosclerosis and decreased compliance of arterial wall and hypertension have close relationship.[Wayne Alexander R, 1995] Several causes have been attributed to the pathophysiology of hypertension and atherosclerosis, which include oxidative activation of endothelial lining, inflammation, hypercholesterolemia and other forms of dyslipidemia.[Gao J, et al., 2011] Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency [Sliz D, et al., 2010]. Many prospective and retrospective epidemiological studies have shown that high plasma levels of lipoprotein are independent risk factors for atherosclerosis and its complications. This association was also confirmed by Helsinki heart study and physician health study [William P, et al., 1992]. Statins are the most widely used drugs for lowering cholesterol levels. This class of drug is believed to be vastly beneficial for reducing cholesterol and thus reducing chances of atherosclerotic changes in the blood vessels [Syed M Ahmed, et al.,1998]. Credit has been accorded to this drug for saving millions of lives. Even those without any cardiovascular disorders may be prescribed statins as primary prophylaxis [Aronow WS, 2001, 2003]. More than 100 years ago a German pathologist named Rudolf Virchow discovered that cholesterol was to be found in the artery walls of people that died from occlusive vascular diseases, like myocardial infarction. Cholesterol was found to be responsible for the thickening of the arterial walls and thus decreasing the radius in the arteries which leads in most cases to hypertension and increased risk of occlusive vascular diseases [Smilde TJ, et al., 2000].

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Statins block the cholesterol synthesis pathway by inhibiting HMG CoA reductase. Statins inhibit cholesterogenesis in the liver [Joel G Hardman, et al., 2001]. Statins have been shown to have many other pleotropic actions too, which include anti-inflammatory, immune-modulating, anti-oxidant, vascular cytoprotection, angiogenesis, plaque stability, endothelial function, anti-thrombotic etc. [Mihos CG, et al., 2010; Liao JK, 2002]. Inhibition of cholesterol synthesis in other organs than liver could be harmful.Therefore statins must be hydrophilic. Hydrophilic statins have more specificity on hepatocytes. Lipophilic statins could produce more harmful side effects due to its diffusion onto other tissues. Of the marketed statins, Ceruvastatin was the most lipophilic and also had the largest percentage of serious adverse effects due to its ability to inhibit vascular smooth muscle proliferation and as a result was voluntarily removed from the market by the manufacturer [White, CM, 2002]. Carotid artery intima-media thickness (CIMT) is a marker of cardiovascular disease associated with incidence of stroke. Carotid intima media thickness testing is recognized as a valid method for the non-invasive assessment of atherosclerosis [Polak JF, et al., 2011]. The normal Carotid intima-media thickness ranges from 0.05-0.08cm (0.5-0.8 cm) [Carol. M, et al., 2004]. Arterial wall thickness and compliance are important factors in hemodynamics. However decrease in the wall strength and increased compliance could not be always considered a positive factor. It has been observed that a number of patients are being diagnosed with abdominal aortic aneurism and cerebrovascular hemorrhage lately. Reduction of smooth muscle proliferation and reduced cholesterol levels could reduce CIMT and the strength of the vessel wall. Hence in the present study we investigate the wall thickness of hypertensives on statin therapy which could be an indicator of vessel wall strength.

MATERIALS AND METHODS

Forty hypertensive patients (HT), twenty of them were not administered statins for lowering cholesterol (Group I, n=20; 11 Females Gr Ia, and 9 Males, Gr Ib) and a similar number (Group II, n=20; 10 Females – Gr IIa, and Males Gr IIb) who were taking cholesterol lowering medication for more than one year and age matched 'control' subjects have been included in this study. The groups were subdivided into Male and female subjects and their results were compared. The subjects were in the age group of 50-70 years.

Ultrasound analysis of the vessel wall thickness was done using GE Voluson 730 Expert (Ultrasound Machine). Low frequency: 3.5-5.5 M Hz. High penetration power was used (Fig.1).

Right (Rt CCA) and left (Lt CCA) common carotid artery thickness (in cm) was measured [Ludwig M, et al., 2003]. Age, sex, Blood pressure, treatment history of the subjects were recorded. Statistical analysis of the data was done using Student's 't' test and ANOVA; $p<0.05$ is accepted as statistically significant.

An informed consent was obtained from the subjects by explaining the procedure thoroughly before including them in the study.

Institutional ethics committee clearance was obtained before the start of this project.

Inclusion/exclusion criteria:

Inclusion criteria: Hypertensive patients (Group I) with abnormal lipid profile not on statins.

Hypertensive patients (Group II) were on long term statin therapy. (Atorvastatin, dosage 10-20 mg/day).Age group above 18 years.

Exclusion criteria: Diabetic patients, pregnant women, people aged below 18 years

RESULTS

Arterial wall thickness in both right and Left common carotid arteries among controls, hypertensives on statin therapy and hypertensive subjects who are not on statin therapy, (mean ± SD) are shown in Table 1. Arterial wall thickness showed significant variations among the groups. (ANOVA: $F=57.319$, $p<0.001$ for Right Common Carotid; $F= 49.508$, $p< 0.001$ for Left Common Carotid Artery).

The wall thickness (I-M) in the group of Hypertensive patients who were on treatment with statins was comparable to the control (normotensives). But the wall thickness among the hypertensive patients (who were not on statins) showed significantly increased value ($p<0.001$). Table 2.

Comparison of the CIMT among male and female subjects showed a similar trend wherein, the CIMT was reduced in statin treated hypertensive subjects while in the untreated subjects, the thickness was more. Table 3.

There was no significant difference among the male and females in the same group Viz. Control, HT Or HT+ statin groups.

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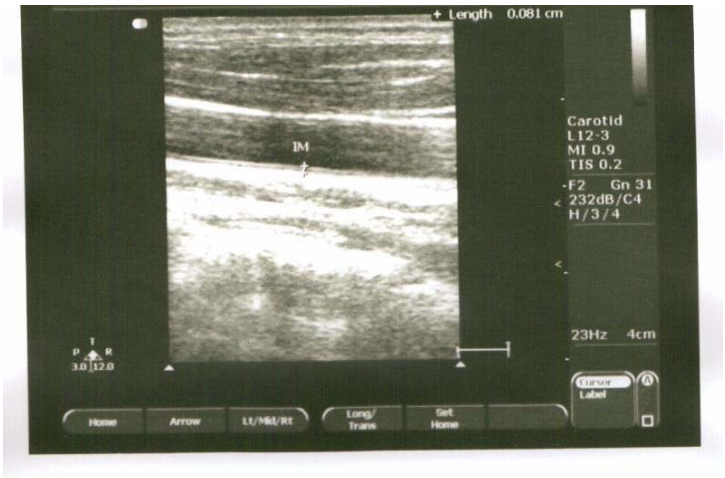

Figure 1: The Carotid artery wall-Ultra sound image in a hypertensive male patient.

Table 1: RCA & LCA thickness in control, untreated hypertensive (Group I) and Statin treated hypertensive patients(Group II). Values in cm±SD.

		N	Mean	Std. Deviation
Rt_CCA	Control	20	0.0615	0.01755
	HT not on Statin	20	0.1110 ††**	0.01804
	HT on statin	20	0.0570††**	0.01750
Lt_CCA	Control	20	0.0655	0.01638
	HT not on Statin	20	0.1140††**	0.02210
	HT on statin	20	0.0635 ††**	0.01531

****Control Vs HT p<0.001, Control Vs HT + Stat – NS, ** HT VsHT+Stat – Sig. p<0.001**
Intergroup difference: †† p< 0.001

Table 2: Statistical analysis of results of arterial wall thickness among the three groups.

Dependent Variable	Statin status	Statin status	Mean Difference	p	95% Confidence Interval	
					Lower Bound	Upper Bound
Rt_CCA	Control	HT on Statin	.00450	.702	-.0090	.0180
		HT not on statin	-.04950*	.001	-.0630	-.0360
	HT on Statin	Control	-.00450	.702	-.0180	.0090
		HT not on statin	-.05400*	.001	-.0675	-.0405
	HT not on statin	Control	.04950*	.001	.0360	.0630
		HT on Statin	.05400*	.001	.0405	.0675
Lt_CCA	Control	HT on Statin	.00200	.936	-.0118	.0158
		HT not on statin	-.04850*	.001	-.0623	-.0347
	HT on Statin	Control	-.00200	.936	-.0158	.0118
		HT not on statin	-.05050*	.001	-.0643	-.0367
	HT not on statin	Control	.04850*	.001	.0347	.0623
		HT on Statin	.05050*	.001	.0367	.0643

* The mean difference is significant at the .05level.

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Table 3: RCA & LCA thickness in Male and Female subjects among control, Statin untreated, treated and hypertensive patients. Values in cm±SD. Hypertensive subjects showed significantly higher thickness of the wall. ** p<0.01

Gr	Age	RCA	LCA
Control-Females (n=10)	57.1±8.2	0.05±0.01	0.06±0.02
Control-Males (n=10)	59.6±15.1	0.07±0.02	0.07±0.02
Ia – HT - Females(n=9)	69.36±8.17	0.12±0.02	0.12±0.1
Ib – HT - Males(n=11)	61.11±10.5	0.10±0.01	0.11±0.03**
IIa – HT +st - Females(n=10)	63.5±9.7	0.06±0.007**	0.068±0.010 **
IIb – HT +st - Males(n=10)	54.08±10	0.05±0.02**	0.06±0.02**

DISCUSSION

Treatment with statins found acceptance among the clinicians to reduce the LDL cholesterol and thus show beneficial effect in the prevention of atherosclerotic changes in the arterial wall. Lipid lowering action of the statins is the main reason for suggestion of advising statins to all patients above middle age, even without any known cardiovascular symptoms.[Aronow WS, 2001, 2003] .

In the present study we analyzed the arterial wall thickness variations caused by the effect of statins by ultrasonological assessment of Intima-Media thickness. Our results are in agreement with the available literature, which showed a significant decrease in the Intima/media thickness in those patients treated with statins over a long term. We believe that since the cholesterol forms integral part of all tissues, drastic reduction in cholesterol levels could adversely affect the arterial wall anatomy, which may not be restricted to the Intima but also involve the muscular and adventitia layers. We found that the patients with hypertension (untreated with statins) had thicker arterial walls compared to the age matched controls. This is in agreement with the findings found elsewhere in the medical literature [Sliz D, et al.,2010].[19] But researchers have suggested that actions of statins on the vascular wall could be unconnected to the lipid lowering effect of statins. [White, CM, 2002]. Therefore, there is a possibility of reduced smooth muscle proliferation affecting the CIMT. Is thinning of blood vessels physiologically beneficial? Arterial compliance is an important factor which determines the BP. However, thinning of the blood vessels could not be straight away accepted as increase in compliance. It has been reported that two thirds of elderly patients with Abdominal Aortic Aneurysm also had Coronary arterial disease. [Savolainen H, et al., 2010] In hypertensive patients reduced Intima-Media thickness might contribute to reduced rate of coronary arterial diseases. But risks of aneurysm and hemorrhage due to arterial rupture should also be kept in mind while treating the elderly patients with statins. Pleotropic actions of statins attracted attention of the investigators for some time. [Mihos CG, et al., 2010] Therefore study of non-lipid lowering actions such as direct influence on the arterial wall thickness and compliance could be very useful. Scope of present study was limited to evaluation of the radiological measurement of wall thickness of carotid arteries in those patients treated with statins and controls and no follow up study was done. Lipid profile of the patients was not presented in this report. Although cholesterol levels were not compared in this study, normalization of lipid level is unlikely to be the reason for reduction in the intima-media thickness because in general only one fourth of individuals attain lipid targets in spite of treatment in practice settings.[Mihos CG, et al., 2010] Hence the near normalization of intima-media thickness seen in hypertensives in this study raises the possibility of action of statins in the arterial wall beyond correction of dyslipidemia. This possible pleotropic action of statin may be of relevance in the setting of thinning of the arterial wall, which may result in dilatation of large vessels. [Hurks R, et al., 2010] This might be an undesirable effect if it occurs in abdominal aorta or cerebral vessels which might result in increased risk of hemorrhage in elderly individuals. However, reports on effect of statins on abdominal aortic aneurysm were inconclusive [Saratzis A, et al., 2010]. Further investigation into the Physical, histological, biochemical changes in the wall of blood vessels could reveal more information regarding the effects of statins and throw more light on the other pleotropic effects of this class of drugs.

CONCLUSIONS

From this study we concur with the available scientific findings that the use of statins produces a reduction in the Intima-Media thickness. Use of statins is widely accepted as a prophylactic treatment regimen for prevention of CAD and hypertension. Thinning of vessel wall in elderly hypertensives may have undesirable consequences and needs to be studied in greater detail.

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REFERENCES

Aronow WS Hypercholesterolemia. The evidence supports use of statins, Geriatrics. (2003) Aug;58(8):18-20, 26-8, 31-2.

Aronow WS., Cholesterol (2001).Rationale for lipid-lowering in older patients with or without CAD, Geriatrics. 2001 Sep;56(9):22-5, 28-30.

Carol. M. Rumack, Stephanie R Wilson, J. William Charboneau. (2004)Diagnostic Ultrasound Volume 1, Study of extracerebral vessels: Kelly S. Freed M.D, Linda K. Brown M.D, Barbara. A. Carroll M.D. 2nd edition; page no. 888.

Ford ES. (2011). Trends in Mortality From All Causes and Cardiovascular Disease Among Hypertensive and Nonhypertensive Adults in the United States. Circulation, 123 (16): 1737

Gao J, Ishigaki Y, Yamada T, Kondo K, Yamaguchi S, Imai J, Uno K, Hasegawa Y, Sawada S, Ishihara H, Oyadomari S, Mori M, Oka Y, Katagiri H. (2011). Involvement of Endoplasmic Stress Protein C/EBP Homologous Protein in Arteriosclerosis Acceleration With Augmented Biological Stress Responses. Circulation. Aug 16;124(7):830-9. Epub

Hurks R, Hoefer IE, Vink A, Pasterkamp G, Schoneveld A, Kerver M, de Vries JP, Tangelder MJ, Moll FL (2010). Different effects of commonly prescribed statins on abdominal aortic aneurysm wall biology. Eur J VascEndovasc Surg. May;39(5):569-76. Epub 2010 Mar 11.

Joel G Hardman, Lee E Limbird, (2001). Goodman and Gilman's.The pharmacological basis of therapeutics.10th edition; 984-87.

Liao JK. (2002). Beyond lipid lowering: the role of statins in vascular protection. Int J Cardiol. Nov;86(1):5-18.

Ludwig M, von Petzinger-Kruthoff A, von Buquoy M, Stumpe KO. (2003). Intima media thickness of the carotid arteries: early pointer to arteriosclerosis and therapeutic endpoint. Ultraschall Med. 2003 Jun;24(3):162-74. (German), Comment: Ultraschall Med.Jun;24 (3):151-2.

Mihos CG, Salas MJ, Santana O (2010). The pleiotropic effects of the hydroxy-methyl-glutaryl-CoA reductase inhibitors in cardiovascular disease: a comprehensive review. Cardiol Rev. Nov-Dec;18(6):298-304.

Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB (2011). Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis.Stroke. Nov;42(11):3017-21.

Roger VL, Go AS, Lloyd-Jones DM, et al. (2012). Heart disease and stroke statistics update: a report from the American Heart Association. Circulation, 2012 Jan 3;125(1):e2-e220.

Saratzis A, Kitas GD, Saratzis N, Melas N. (2010). Can statins suppress the development of abdominal aortic aneurysms? A review of the current evidence.Angiology. Feb;61(2):137-44.

Savolainen H, Novak J, Dick F, Widmer MK, Carrel T, Schmidli J, Meier B. (2010). Prevention of rupture of abdominal aortic aneurysm.Scand J Surg. 99(4):217-20.

Sliz D, Mamcarz A, Filipiak KJ, Siebert J, Naruszewicz M. (2010). 3ST-POL trial: standards of statin use in Poland in the context of the European Society of Cardiology guidelines. Pol Arch Med Wewn. Sep;120(9):328-33.

Smilde TJ, van Den Berkmortel FW, Wollersheim H, Van Langen H, Kastelein JJ, StalenhoefAf. (2000). The effect of cholesterol lowering on carotid and femoral artery wall stiffness and thickness in patients with familial hypercholesterolaemia.Eur J Clin Invest.30:473-80.

Syed M Ahmed, Mark ClasenE and John F Donnelly.(2010). Management of dyslipidemia in adults. American family physician; Am Fam Physician. May 1;57(9):2192-2204.

Wayne Alexander R, (1995). Hypertension and the Pathogenesis of atherosclerosis Oxidative Stress and the Mediation of Arterial Inflammatory Response: A New Perspective.Hypertension. 25:155-161

White, C. Michael.(2002). "A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin". The Journal of Clinical Pharmacology 42 (9): 963–970.

William P, David S, James L. (1992). Relation of serum lipoprotein levels and Systolic blood pressure to early atherosclerosis. The Bogalusa heart study.New EngJMed. 314(3):138-44.