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# **Original Research Article**

# Study of lipid and non-lipid effects of statins in hypertensive patients

Shashikala E.1\*, Raghawa Rao B. N. V.2

<sup>1</sup>Department of Pharmacology, Gandhi Medical College Hospital, Hyderabad, Telangana, India <sup>2</sup>Department of Medicine, Gandhi Medical College/Gandhi Hospital, Hyderabad, Telangana, India

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### \*Correspondence to:

Dr. Shashikala E., Email: drvijayragava@gmail.com

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#### **ABSTRACT**

**Background:** Hypertension is one of the commonest diseases affecting the mankind which is associated with endothelial dysfunction and left ventricular dysfunction and hence the study is aimed to observe the effects of statins on endothelial and left ventricular dysfunction.

**Methods:** 15 hypertensive patients were given atorvastatin for 4 weeks and compared with sex and aged matched 15 controls after a detailed Clinical history, clinical examination, biochemical investigations, chest X-ray, electrocardiogram, echocardiogram and Doppler study of brachial artery.

**Results:** Both study group and control group consisted of 10 males and 5 females who have dyslipidemia, endothelial and ventricular dysfunction. After a 4 weeks of study, in study group, flow mediated brachial artery diameter (FMD%) increased significantly (11.39%, P<0.01) from 7.37% to 18.76%, mean LV systolic function (EF) improved significantly (10.73%, P:<0.01) from 54.6% to 60.65%, LV diastolic function was normalized in 7 (46.67%) and improved in 5 (33.33%) patients, the mean systolic and diastolic BP decreased significantly (12.03%, P<0.01, 10.29%, P<0.01) from 149.66mmHg to 131.66mmHg and from 90.66mmHg to 81.33mmHg respectively, while in control group FMD increased marginally (1.07%) from 7.50% to 8.57%, LV EF marginally improved (1.47%) to 54.86% from 54.06%; no improvement in diastolic dysfunction, mean systolic and diastolic BP decreased marginally (6.25%, 0.74%) from 149.33 mmHg to 140mmHg and from 90.33mmHg to 89.66mmHg respectively.

**Conclusions:** Statins improve not only lipid profile but also endothelial and LV functions which resulted in significant reduction of systolic and diastolic BP. Hence it is reasonable to treat all hypertensive patients with statins besides concurrent hypertension treatment.

**Keywords:** Atorvostatin, Endothelial dysfunction, Hypertension, Lipid and non-lipid effects, LV dysfunction

# INTRODUCTION

Hypertension is one of the most important public health problems worldwide and if left untreated, 50% die of CAD, 33% die of stroke and 10-15% die of renal failure.<sup>1</sup>

These vascular complications of the Hypertension are mainly due to the damage to vascular endothelium (endothelial dysfunction) caused by shear stress of Hypertension which is the initial event in atherosclerotic process. Hence the present study is aimed at observing the association of the essential hypertension with endothelial dysfunction and left ventricular dysfunction

which are assessed noninvasively and to evaluate the effects of statins (non-lipid effects) on endothelial and left ventricular dysfunction besides their conventional effect on lipid profile.

# **METHODS**

Hypertensive is diagnosed when SBP is ≥140 mm Hg and or DBP is ≥90mm Hg as per JNC-VII criteria, 2003.² Patients with Secondary hypertension, Diabetes mellitus, Hyperlipidemia, Ischemic heart disease and history of smoking were excluded from the study.

After consent from each patient, a detailed Clinical history, Clinical examination, Biochemical investigations (blood sugar, serum creatinine, serum electrolytes and lipid profile), Chest X-ray, Electrocardiogram, Echocardiogram for left ventricular function(systolic and diastolic) and Doppler study of brachial artery for endothelial function(as described by Celemajor et al) were done. The patients in Study group were received atorvastatin (10-20mg/day) for 4 weeks with concurrent hypertension treatment, while Control group patients received only antihypertensive treatment.

BP recording, serum lipid profile, echocardiogram for left ventricular function and Doppler study for endothelial function were repeated after 4 weeks in study and control subjects.

#### **RESULTS**

#### Clinical characteristics

In Study group: the age of the 15 hypertensive patients ranged from 38-65yrs with a mean of 51.33yrs  $\pm 6.72$ with 10 (66.67%) males and 5 (33.33%) females. Similarly Control group consisted of 15 hypertensive patients with age ranging between 36-63yrs with a mean of  $51.13\pm7.29$ , 10 (66.67%) males and 5 (33.33%) females.

The duration of hypertension in Study group ranged between 2-10yrs with a mean of 3.93yrs±2.71while in Control group it ranged between 2-8yr with a mean of 3.86yrs±2.59. Both Study and Control groups have 3 newly detected hypertensive.

### Routine investigations

Both in study and control cases routine biochemical investigations-fasting blood sugar, serum creatinine, and serum electrolytes were within normal limits.

X-ray chest (PA view) and ECG revealed cardiomegaly and left ventricular hypertrophy (LVH) in 6 (40%) study cases with duration of hypertension of  $\geq$ 5yrs. Similarly Cardiomegaly and LVH were present in 5 (33.33%) patients of Control group with duration of hypertension of  $\geq$ 6yrs.

## Lipid profile

Dyslipidemia was present in both groups of patients. After 4 weeks of study, the mean total cholesterol in study group decreased significantly (18.92%, P <0.01) from 227mg/dl to 184mg/dl, while in control group mean total cholesterol decreased marginally (4.81%) from 211.mg/dl to 201mg/dl.

Similarly the mean LDL-C cholesterol in study group decreased significantly (20.74%, P <0.01) from 106 mg/dl to 84 mg/dl, while in control group the mean LDL cholesterol decreased insignificantly (2.99%) to 99mg/dl

from 102. mg/dl. So also the decrease of triglycerides in study group was significant (11.75%, P <0.01) from 159mg/dl to 140mg/dl while this was insignificant (1.38%) in control cases which decreased to 156.mg/dl from 158mg/dl. The initial mean HDL cholesterol in study group was 41 mg/dl and after 4 weeks it has increased significantly (13.94%, P <0.01) to 47mg/dl while in control group the mean HDL cholesterol increased marginally (3.39%) to 42mg/dl from 41mg/dl.

In study group the significant decrease in total cholesterol, LDL-C and triglycerides and increase in HDL-C was more in patients with duration of hypertension of <5yrs as compared to patients with duration of hypertension of ≥5yrs (Table 1).

Table 1: Lipid profile initial vs after 4 weeks.

LIPID Parameters (mean values mg/dl)		Study group	Control group
Total cholesterol	Initial value	227 mg/dl	211 mg/dl
	After 4 wks	184 mg/dl	201 mg/dl
	% of <b>♥</b>	18.92% (P <0.01)	4.81 %
LDL-C	Initial value	106 mg/dl	102 mg/dl
	After 4 wks	84 mg/dl	99 mg/dl
	% of <b>Ψ</b>	20.74% (P <0.01)	2.99%
HDL-C	Initial value	41 mg/dl	41 mg/dl
	After 4 wks	47 mg/dl	42 mg/dl
	% of♠	13.94% (P <0.01)	3.39%
Triglycerid es	Initial value	159 mg/dl	158 mg/dl
	After 4 wks	140 mg/dl	156 mg/dl
	% of <b>Ψ</b>	11.75% (P <0.01)	1.38%

### Endothelial function

In study group the reactive hyperemia induced brachial artery diameter improved significantly (15.57%, P<0.01) to 4.23mm from 3.66mm,while in control group there was marginal increase (3.24%) 3.70mm to 3.82mm.

In study group Flow mediated brachial artery diameter (FMD%) increased significantly (11.39%, P<0.01) from 7.37% to 19.18%, while in control group this increased marginally (1.07%) from 7.50% to 8.57%.

Similarly patients with long standing hypertension (≥5yrs) show less response to %FMD in both study and control groups (Figure 1 and Table 2).

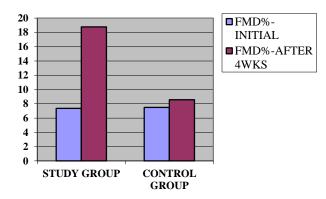


Figure 1: Endothelial function: FMD % in study and control cases.

Table 2: Endothelial function initial vs after 4 weeks.

Parameter		Study group	Control group
Mean Brachial	Initial value	3.42	3.45
artery Diameter (mm)	After 4 weeks	3.55	3.52
	% of <b>↑</b>	3.82%	2.02%
Mean Brachial	Initial	3.66	3.70
artery diameter after	After 4 weeks	4.23	3.82
reactive hyperemia (mm)	% of <b>↑</b>	15.57% (P <0.01)	3.24%
Mean Flow	Initial	7.37%	7.50%
Mediated Dilatation (FMD	After 4 weeks	19.18%	8.57%
in %) of Brachial artery	% of <b>↑</b>	11.39% (P <0.01)	1.07%

# Left ventricular function

The mean LV systolic function (EF) in study group was 54.6% which improved significantly (10.73%, P: <0.01) to 60.65% and mild LV systolic dysfunction (EF<50) detected initially in 2 (13.33%) patients was normalized with improvement in EF to >50%. However in control group it marginally improved (1.47%) to 54.86% from 54.06% and mild LV systolic dysfunction (EF<50) detected initially in 2 (13.33%) patients was not improved.

Initial assessment of LV diastolic function detected diastolic dysfunction in 12 (80%) patients each of study and control groups. However in study group LV diastolic function was normalized in 7 (46.67%) patients and 5 (33.33%) patients showed improvement from moderate to mild diastolic dysfunction after 4 weeks. However in

control group there was no improvement in diastolic dysfunction.

The significant improvement of LV systolic and diastolic functions after therapy with atorvastatin in study group was more in patients with duration of hypertension <5yrs as compared to patients with duration of  $\ge5$ yrs (Figure 2, 3 and 4 and Table 3).

Table 3: LV function initial Vs after 4 weeks.

Parameters		Study	Control
1 at afficiets		group	group
LV Systolic Function (EF %)	Initial	54.6	54.06
	After 4 wks	60.46	54.86
	% of <b>↑</b>	10.73% (P:<0.01)	1.47%
LV Systolic dysfunction (EF<50%)	Initial	2 (13.33%)	2 (13.33%)
	After 4 wks	nil	2 (13.33%)
LV Diastolic dysfunction -mild	Initial	7 (66.67%)	8 (53.33%)
	After 4 wks	5 (33.33%)	8 (53.33%)
LV	Initial	5 (33.33%)	4 (26.67%)
Diastolic dysfunction -moderate	After 4 wks	nil	4 (26.67%)

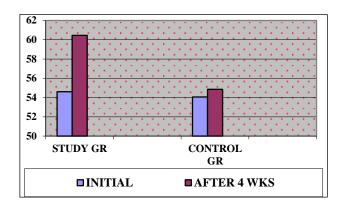


Figure 2: LV systolic function (EF %) in study and control cases.

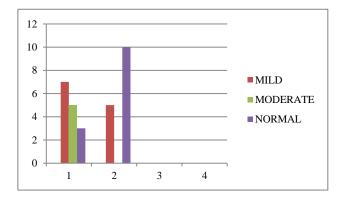


Figure 3: LV diastolic dysfunction in study cases.

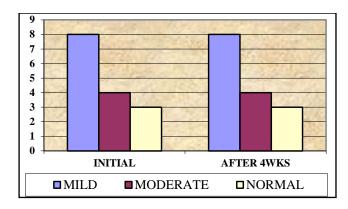


Figure 4: LV diastolic dysfunction in control cases.

#### **Blood** pressure

The mean systolic BP in study group decreased significantly (12.03%) to 131mmHg from 149mm Hg after 4 wks of atorvastatin and concurrent hypertension treatment, while in control group it decreased marginally (6.25%) from 149 mmHg to 140mm Hg after 4 weeks of hypertension treatment but without atorvastatin therapy.

Similarly the mean diastolic BP in study group was 90mmHg which decreased significantly (10.29%, P<0.01) from 90mmHg to 81mm Hg, while in control group it decreased marginally (0.74%) from 90mmHg to 89mmHg (Table 4).

Table 4: Blood pressure (BP) initial Vs after 4 weeks.

Parameter	S	Study group	Control group
Mean systolic BP (mmHg)	Initial value	149	149
	After 4 weeks	131	140
	% of <b>♥</b>	12.03% (P:<0.01)	6.25%
Mean diastolic BP (mmHg)	Initial	90	90
	After 4 weeks	81	89
	% of <b>♥</b>	10.29% (P:<0.01)	0.74%

# **DISCUSSION**

#### Lipid effects of statins

In the present study there was significant effect on lipid profile in study cases that were given atorvastatin for 4 weeks with concurrent treatment of hypertension. Similar observations were reported by ASCOT, MIRACL, PROVE-IT and CURVES trials.<sup>5-8</sup>

# Non-lipid effects of statins: on endothelial function

Present study indicates endothelial dysfunction in all the patients of both the groups (FMD% in Study gr: 7.37%, Control gr: 7.50%, Normal: is ≥18.5%) which is similar

to previous studies of Kelm M, et al, Iiyama et al, Li J et al, Hunan et al and Atkov et al. The pathogenesis for endothelial dysfunction in hypertensive patients is due to;

- Physical stress (shear stress of hypertension) that can alter hemorrheology, and cause mechanical damage to endothelial cells leading to endothelial dysfunction.
- 2. Similarly dyslipidaemia is associated with the loss of endothelium dependent dilatation as oxidized LDL and small dense LDL affect the endothelial NO bioavailability.<sup>14</sup> So also remnant particles formed from chylomicrons and VLDL are highly atherogenic and are associated with endothelial dysfunction and reduced NO.<sup>15</sup>

In the present study patients treated with atorvastatin for 4 weeks in study group showed greater increase in FMD% as compared to patients without atorvastatin in control group (18.76 Vs 8.57%) (P<0.01). The significant change in the lipid profile with atorvastatin therapy has contributed to the drastic improvement in the endothelial function.

This potential effect of statins in the improvement of endothelial function in the present study was also reported by previous studies of Lueng WH et al in hypercholesterolemic patients, O' Driscoll G et al with simvastatin, Treasure CB et al with lovastatin and Egashira K et al with pravastatin. <sup>16-19</sup>

#### Non-lipid effects of statins: on lv function

In the present study there was LV dysfunction in most of the patients in both groups which was also reported in previous studies of Frohlich ED et al, Dunn FG et al, Dreslinski GR et al, Inouye I et al and Fouad FM et al. 20-24

The significant improvement in LV systolic and diastolic functions in the study cases (P<0.01) as compared to control group in the present study is due to;

- 1. Significant improvement in endothelial function and
- Significant decrease in systolic and diastolic BP after therapy with atorvastatin and concurrent use of antihypertensives.

# Non-lipid effects of statins: on BP

The significant decrease of systolic and diastolic BP (P<0.01) in the present study in study cases as compared to control group could be due to significant improvement in endothelial function, left ventricular function and lipid profile.

#### **CONCLUSION**

 Present study showed dyslipidemia, endothelial and ventricular dysfunctions occur in most patients of hypertension. Hence all hypertensive patients should be investigated for dyslipidemia besides routine investigations and followed up for brachial artery endothelial function and LV function at least every 3 months.

- Present study showed not only improved lipid profile in hypertensive patients but also improved endothelial and LV functions which resulted in significant reduction of systolic and diastolic BP as compared to controls.
- Hence it is reasonable to treat all hypertensive patients with statins besides concurrent hypertension treatment for the improvement in the lipid profile, endothelial and ventricular functions which is manifested clinically as significant reduction in systolic & diastolic BP and thereby preventing and reducing complications of hypertension including coronary heart disease, heart failure, stroke and mortality.
- All treatment modalities should be started early as beneficial effects in chronic hypertensive patients are less.

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