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 149.66 mmHg to 131.66 mmHg and from 90.66 mmHg to 81.33 mmHg 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 140 mmHg and from 90.33 mmHg to 89.66 mmHg 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: Atorvastatin, 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.1

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 ≥90 mm 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±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±7.29, 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±2.71 while 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 ≥5yrs. Similarly Cardiomegaly and LVH were present in 5 (33.33%) patients of Control group with duration of hypertension of ≥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 227 mg/dl to 184 mg/dl, while in control group mean total cholesterol decreased marginally (4.81%) from 211 mg/dl to 201 mg/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 99 mg/dl from 102 mg/dl. So also the decrease of triglycerides in study group was significant (11.75%, P <0.01) from 159 mg/dl to 140 mg/dl while this was insignificant (1.38%) in control cases which decreased to 156 mg/dl from 158 mg/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** | **Study group** | **Control group** |
|----------------------|----------------|------------------|
| **Initial value** | 227 mg/dl | 211 mg/dl |
| **After 4 wks** | 184 mg/dl | 201 mg/dl |
| **% of ↓** | 18.92% (P <0.01) | 4.81% |
| **Total cholesterol** | | |
| **Initial value** | 106 mg/dl | 102 mg/dl |
| **After 4 wks** | 84 mg/dl | 99 mg/dl |
| **% of ↓** | 20.74% (P <0.01) | 2.99% |
| **LDL-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% |
| **HDL-C** | | |
| **Initial value** | 159 mg/dl | 158 mg/dl |
| **After 4 wks** | 140 mg/dl | 156 mg/dl |
| **% of ↓** | 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).

Table 2: Endothelial function initial vs after 4 weeks.

| Parameter                                      | Study group | Control group |
|------------------------------------------------|-------------|---------------|
| Mean Brachial artery Diameter (mm)             | Initial     | 3.42          | 3.45          |
|                                                | After 4 weeks | 3.55          | 3.52          |
| % of ↑                                          | 3.82%       | 2.02%         |
| Mean Brachial artery diameter after reactive hyperemia (mm) | Initial     | 3.66          | 3.70          |
|                                                | After 4 weeks | 4.23          | 3.82          |
| % of ↑                                          | 15.57% (P <0.01) | 3.24%         |
| Mean Flow Mediated Dilatation (FMD in %) of Brachial artery | Initial     | 7.37%         | 7.50%         |
|                                                | After 4 weeks | 19.18%        | 8.57%         |
| % of ↑                                          | 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 ≥5yrs (Figure 2, 3 and 4 and Table 3).

Table 3: LV function initial Vs after 4 weeks.

| Parameters                                      | Study group | Control group |
|------------------------------------------------|-------------|---------------|
| LV Systolic Function (EF %)                     | Initial     | 54.6          | 54.06         |
| % of ↑                                          | 10.73% (P<0.01) | 1.47%         |
| LV Systolic dysfunction (EF<50%)                | Initial     | 2 (13.33%)    | 2 (13.33%)    |
| LV Diastolic dysfunction -mild                  | After 4 wks | nil           | 2 (13.33%)    |
| LV Diastolic dysfunction -moderate              | Initial     | 5 (33.33%)    | 4 (26.67%)    |
|                                                | After 4 wks | nil           | 4 (26.67%)    |
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).

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.6-19

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
2. 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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REFERENCES

1. Kaplan NM. Systematic hypertension. Mechanisms and Diagnosis. In Braunwald’s Heart disease 5th ed. Philadelphia: W. B. Saunders Company. 1997:26:807-40.

2. Chobanian AV, Bakris GL, Black HR. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003;289:2560-72.

3. Rakowskiv H, Appleton C, Chan KL. Canadian consensus recommendations for measurement and reporting of diastolic dysfunction by echocardiography. J Am Soc Echocardiogr. 1996;9:736-60.

4. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI. Noninvasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340:1111-15.

5. Sever PS, Dahlof B, Poulter NR. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower the average cholesterol concentrations, in the Anglo Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): A multicentre randomized controlled trial. Lancet. 2003;361:1149-58.

6. Schwartz GG. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndrome. The MIRCL study: a randomized control trial. JAMA. 2001;285:1711.

7. Cannon CP. Intensive versus moderate lipid lowering with statins after acute coronary syndrome: PROVE-IT trial. N Eng J Med. 2004;350:1945-504.

8. Jones PH, Kafonek S, Laurora I. Comparative dose efficacy study of atorvastatin with that of lovastatin, pravastatin, simvastatin and fluvastatin in patients with hypercholesterolemia: The CURVES study. Am J Cardiol. 1998;81:582-7.

9. Kelm M, Preik M, Hafner DJ, Strauer BE. Evidence for a multifactorial process involved in the impaired flow response to nitric oxide in hypertensive patients with endothelial dysfunction. Hypertension. 1996;27:346-53.

10. Iiyama K, Nagano M, Yo Y, Nagono N, Kamide K. Impaired endothelial function with essential hypertension assessed by ultrasonography. Am Heart J. 1996;132:77-82.

11. Li J, Zhao SP, Li XP, Zhuo QC, Gao M, Lu SK. Noninvasive detection of endothelial dysfunction in patients with essential hypertension. Int J Cardiology. 1997;61:165-9.

12. Hunan Y, Ke D. Noninvasive detection of endothelial dependent dilation dysfunction in patients with essential hypertension. Xue Xue Bao. 1998;23(6):590-2.

13. Atkovo OY, Balahonova TV, Pogorelova OA. Noninvasive USG Detection of endothelial function. Eur J Ultrasound. 1998;7(1):37-45.

14. Kinlay S, Selwyn AP, Delargrane D. Biological mechanisms for the clinical success of lipid lowering in coronary artery disease and the use of surrogate end points. Curr Opin Lipidol. 1996;7:389-97.

15. Inoue T, Saniabadi AR, Matsunaga R. Impaired endothelial dependent acetylcholine induced coronary artery relaxation in patients with high serum remnant lipoprotein particles. Atherosclerosis. 1998;139:363-7.

16. Leung WH, Lau CP, Wong CK. Beneficial effect of cholesterol lowering therapy on coronary endothelium dependent relaxation in hypercholesterolaemic patients. Lancet. 1993;341:1496-1500.

17. O’Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-Coenzym A reductase inhibitor, improves endothelial function within 1 month. Circulation. 1997;95:1126-31.

18. Treasure CB, Klein JL, Weintraub WS. Beneficial effects of cholesterol lowering therapy on the
coronary endothelium in patients with coronary artery disease. N Engl J Med. 1995;332:481-7.
19. Egashira K, Hiroka Y, Kai H. Reduction in serum cholesterol with pravastatin improves endothelium dependent coronary vasomotion in patients with hypercholesterolemia. Circulation. 1994;89:2519-24.
20. Frohlich ED, Tarazi RC, Dustan HP. Clinical-physiological correlations in the development of hypertensive heart disease. Circulation. 1971;4:446-55.
21. Dunn FG, Chandraratna P, de Carvalho JGR, Basta LL, Frohlich ED. Pathophysiologic assessment of hypertensive heart disease with echocardiography. Am J Cardiol. 1977;39:789-95.
22. Dreslinski GR, Frohlich ED, Dunn FG, Messerli FG, Suarez DH, Reisin E. Echocardiographic diastolic ventricular abnormality in hypertensive heart disease: Atrial emptying index. Am J Cardiol. 1981;47:1087-90.
23. Inouye I, Massie B, Loge D, Topic N, Silverstein D, Simpson P. Abnormal left ventricular filling: An early finding in mild to moderate systemic hypertension. Am J Cardiol. 1984;53:120-6.
24. Fouad FM, Slominski JM, Tarazi RC. Left ventricular diastolic function in hypertension: Relation to left ventricular mass and systolic function. J Am Coll Cardiol. 1984;3:1500-6.

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