OBSERVATIONAL STUDY SHOWING INDIRECT EVIDENCE OF VASODILATOR ANTIHYPERTENSIVE CONCOMITANT THERAPY WITH ATORVASTATIN PRECIPITATING DIABETES MELLITUS IN OPD PATIENTS OF TERTIARY CARE HOSPITAL

KEY WORDS: diabetes, amlodipine, atenolol, enalapril

Introduction:
The statins are the most effective and best-tolerated agents for treating dyslipidemia. Various studies have suggested that statins may be associated with a higher incidence of new cases of diabetes. Meta-analysis study of 3 randomized trial, TNT (Treating to New Targets) trial, IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), SPARCL (Stroke Prevention by Agressive Reduction in Cholesterol Levels) trial where TNT trial showed the incidence of NOD with atorvastatin 80 mg and 10 mg was 9.24% and 8.11% respectively. On the other hand, Post hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) showed the relationship between statins and diabetes and showed that pravastatin was associated with a 30% reduced risk of new onset diabetes compared with placebo (OR = 0.70).

At our tertiary care hospital, it was observed that atorvastatin was prescribed in patients of hypertension and heart disease as a concomitantly administered drug along with amlodipine, atenolol, enalapril each of these combined with low dose aspirin. We planned a study to see which antihypertensive causes higher percentage of incident diabetes mellitus when combined with atorvastatin.

Material and methods:
Records of 536 patients receiving amlodipine, atenolol, enalapril for hypertension with altered lipid profile were collected from HMIS, Government Medical College Akola. Data of these patients was collected and analyzed for diabetes mellitus development with concomitant atorvastatin therapy. It was observed that amlodipine, enalapril plus low dose aspirin receiving patients developed diabetes mellitus when concomitantly atorvastatin was being taken (22 out of 268 against 2 patients out of 268 who developed diabetes with atorvastatin with low dose aspirin-total 22 out 268 i.e 8.20 %). There were 17 patients on amlodipine enalapril plus aspirin. 3 were on atenolol and aspirin. The difference among these being i.e 7.4 % is statistically significant. The incident diabetes with vasodilator plus aspirin plus atorvastatin was found to be 6.3 %. This observation gives indirect clue that vasodilator (amlodipine, enalapril plus low dose aspirin plus atorvastatin may cause diabetes mellitus).

Observations and results:
Table 1 and Fig 1: showing incident diabetes in control group (without atorvastatin) receiving antihypertensive and low dose aspirin

<table>
<thead>
<tr>
<th>Concomitant Drug Therapy</th>
<th>Control Group</th>
<th>No of patients who developed DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>171</td>
<td>2</td>
</tr>
<tr>
<td>Atenolol</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Enalapril</td>
<td>33</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2 and Fig 2: showing incident diabetes mellitus in test group patients receiving antihypertensive plus low dose aspirin plus atorvastatin (10 mg and 20 mg)

<table>
<thead>
<tr>
<th>Concomitant Drug Therapy</th>
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</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>177</td>
<td>17</td>
</tr>
<tr>
<td>Atenolol</td>
<td>62</td>
<td>3</td>
</tr>
<tr>
<td>Enalapril</td>
<td>31</td>
<td>2</td>
</tr>
</tbody>
</table>
Another 2 patients who were receiving digoxin plus low dose aspirin who developed incident diabetes mellitus are not included in above table 2

From table of observations it is evident that the patient of control group 5 out of 268 developed incident diabetes mellitus. These patients were not receiving antihypertensive. In table 2 i.e test group 17 patients receiving amlodipine plus low dose aspirin plus atorvastatin, 2 patients receiving enalapril plus low dose aspirin plus atorvastatin, and 3 patients receiving atenolol plus low dose aspirin plus atorvastatin- overall total 22 patients receiving antihypertensive and 2 more patients (not shown in table receiving digoxin along with low dose aspirin have developed incident diabetes after mean duration of 18 months of treatment. Overall 19 patients out of 24 who developed incident diabetes have received indirect vasodilators antihypertensive.

Discussion:
Sampson et al. proposed that the effects of statins on new onset diabetes may centre on altered insulin secretion rather than insulin sensitivity via multiple mechanisms that compromise the functions of pancreatic beta cells. The hypothetical paradigm proposed involves (i) inhibition of intracellular glucose arrival via glucose transporter (GLUT2) which initiates the cascades for insulin secretion, (ii) inhibition of glucokinase by plasma derived cholesterol which is in abundance when de novo synthesis of cholesterol is inhibited, (iii) reduction in ATP production due to suppression of ubiquine (CoQ10) leading to inhibition of insulin secretions, (iv) suppression of isoprenoid synthesis causing down-regulation of the glucose transport system (GLUT4) which is important in glucose uptake, (v) the pro-inflammatory and oxidative effects of plasma derived cholesterol and (vi) induction of beta cell apoptosis due to cytokine-induced over production of nitric oxide.

Lipophilic statins (atorvastatin, simvastatin) particularly high dose, inhibit glucose-stimulated elevations of free Ca in the cytoplasm of beta cells and interferes isoprenoid biosynthesis, thus may cause impaired insulin secretion and exacerbation of insulin resistance. In a study done on the effects of various statins on the glucose-transporter-4, atorvastatin but not other statins seemed to have a detrimental effect on glucose-stimulated elevations of free Ca in the cytoplasm of beta cells. It is beyond the scope of this study to establish a correlation between indirect vasodilator antihypertensive with atorvastatin to produce diabetes in baseline non-diabetics subjects. This requires to be confirmed by other studies. We therefore suggest to avoid combination of indirect vasodilator with atorvastatin in maintenance dose therapy which is required to given for longer time (more than 12 months). However for the purpose of controlling the altered lipid profile in needy patients, pravastatin can be preferred over atorvastatin.

Conclusion:
Atorvastatin should better be avoided in combination with indirect vasodilator in needy patients for the risk of developing incident diabetes which have been observed in this study as 8.2 %.

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Conflict of interest: Nil

References: