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Short Communication

Increase in Glycosylated Haemoglobin (HbA1c) or Diabetes Risk and Use of Statin

Surjit Singh[1*], Pradeep Dwivedi[1], Jaykaran Charan[1], Bharti Bhandari[2] and Preeti Sidhu[3]

1Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, India

2Department of Physiology, All India Institute of Medical Sciences, Jodhpur, India

3Department of Radiology, All India Institute of Medical Sciences, Jodhpur, India

Statins and Diabetes Risk

There has been change in the safety information by United States Food and Drug Administration (US FDA) with regard to the statin use. Recently, there has been concern for increase in fasting plasma glucose levels with the use of statins. Labeling information of the statins like Rosuvastatin has been modified as "Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including Rosuvastatin" [1].

Review of the literature has highlighted the concern. The study done by, Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) review group has reported a 27% increase in Diabetes Mellitus (DM) with the use of rosuvastatin as compared to placebo [2]. A Women's Health Initiative (WHI) study data analysis, reported that statin therapy (Pravastatin, Fluvastatin, Simvastatin, Lovastatin and Atorvastatin) was associated with 48% increased risk of new-onset diabetes in postmenopausal women after adjustment for age and ethnicity and concluded that it is a class effect [3]. Study done by Liew et al., 4 of 1060 subjects revealed 29% (adjusted OR = 1.290, p = 0.044, 95% CI 1.006, 1.654) increased risk of higher HbA1c levels with the use of statin as compared to no statin use.

PubMed and Google Scholar search identified about 14 clinical trials which has evaluated the incidence of diabetes events in the subjects receiving statin therapy. A meta-analysis by Sattar et al., of 13 statin trials with 91,140 participants, reported that statin therapy was associated with a 9% increased risk for incident diabetes (Odds Ratio [OR] 1.09; 95% Confidence Interval [CI] 1.02-1.17), with little heterogeneity (I2=11%) between trials [5]. Similar meta-analysis by Rajpathak et al., of 6 statin trials with 57,593 participants, reported a small increase in diabetes risk (Relative Risk [RR] 1.13; 95% CI 1.03-1.23), with no evidence of heterogeneity across trials [6]. Meta-analysis by Preiss et al., of 5 statin trials with 32,752 participants, revealed a 16% decrease in incident cardiovascular events but a 12% (Odds Ratio [OR] 1.12; 95% Confidence Interval [CI] 1.04-1.22) increase in risk of incident diabetes with the intensive statin therapy as compared to moderate statin therapy [7]. Meta-analysis of 14 clinical trials as done by us, revealed a 30% increased risk of incident diabetes with the use of statins (Figure 1) [2,3,8-19]. Subgroup analysis revealed that Pravastatin, Atorvastatin, Simvastatin, Rosuvastatin, Lovastatin and Fluvastatin was associated with 22%, 30%, 30%, 17%, 44% and 81% increased risk of incident diabetes respectively. As the heterogeneity is large (I2 = 80), we used random effect model for meta-analysis of the studies. Deleting the data of WHI study from the meta-analysis decreases the heterogeneity to 11% but has resulted in decrease in power of meta-analysis. So we did analysis including the WHI study.

***Corresponding author:** Surjit Singh, Department of Pharmacology, All India Institute of Medical Sciences, 342005, Jodhpur, India, Tel: +91 8003996895; E-mail: sehmby_ss@yahoo.com, ss.sehmby@gmail.com

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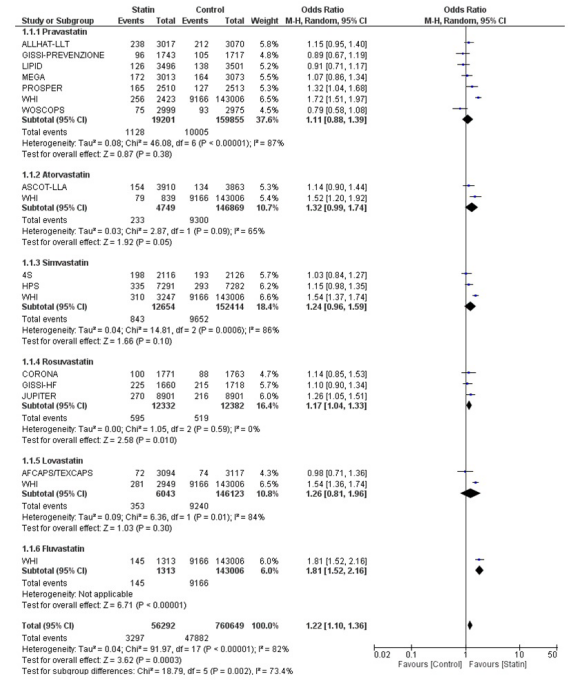

Figure 1: Association between Statin therapy and Incident Diabetes Mellitus.

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The proposed mechanism with regard to hyperglycemia includes inhibition of isoprenoid synthesis and down regulating C/EBPα production [20]. This leads to down regulation of GLUT4 expression on adipocytes, decreasing insulin-mediated glucose uptake and intolerance to glucose. In addition, overproduction of nitric oxide can lead to beta cell apoptosis and decrease in insulin secretion. Statins by inhibiting HMG-CoA reductase cause decrease production of Farnesyl Pyrophosphate (FPP), hence suppression of ubiquinone (CoQ10) synthesis resulting in decreased ATP production and decrease insulin secretion (Figure 2) [20]. Inhibition of HMG-CoA reductase also impair post-receptor insulin and IGF (Insulin Growth Factor-1) phosphorylation and signaling by decrease Mevalonate and other metabolites. Decreased dolichol production cause decrease glycosylation and membrane translocation of mature insulin receptors. Decrease Geranylgeranyl Pyrophosphate impair GLUT-4 expression on adipocytes resulting in insulin resistance. Statins by decreasing adiponectin levels may result in higher tissue IL-6, TNF-α leading to beta cell apoptosis and increased insulin resistance. Other possible mechanisms is, statins inhibiting leptins levels negatively affects *ß-cell* proliferation and insulin secretion. All these mechanisms culminate to development of DM with the use of statins.

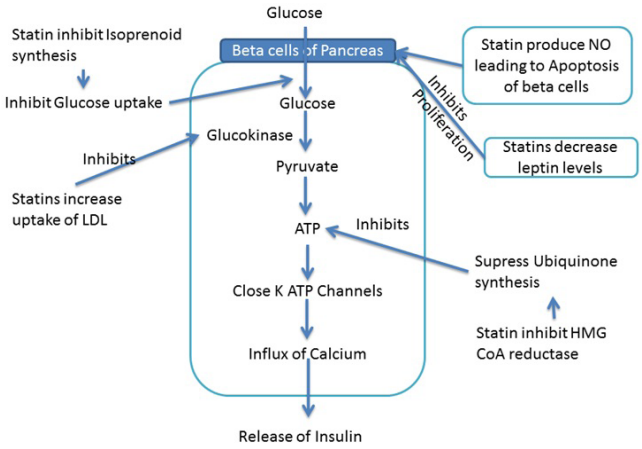

Figure 2: Mechanisms of Action of Statins on beta cells of pancreas resulting in Increase in HbA1c.

Decrease beta cell proliferation - Statins decrease leptin levels which inhibits the proliferation of beta cells of pancreas; Decrease in Insulin release - Statins inhibit isoprenoid synthesis resulting in decreased glucose uptake into beta cells; Statins increases LDL uptake leading to inhibition of glucokinase; Statins by inhibiting ubiquinone synthesis results in decrease ATP generation.

HMG-CoA: 3-hydroxy-methylglutaryl coenzyme A; NO: Nitric oxide; LDL: Low-density lipoprotein

Recommendation for use of Statins in Diabetes

The risk-benefit assessment is necessary for recommendation of use of statins in diabetes patients. In DM patients with CVS risk factors, statins prevent CVS event 8 times more likely than causing a case of incident diabetes [21]. Therefore, a modest increase in blood glucose is not a cause of concern as they decrease morbidity and mortality due to macrovascular and microvascular complications. In patients with low CVS risk factors, lifestyle modifications should be considered and use of statins should be used for less aggressive management of LDL-cholesterol. Meta-analysis by Mihaylova et al., of 27 randomized trials in patients with low risk of vascular disease, statins reduce risk of CVS events and all-cause mortality by 15% and 9% respectively [22].

Study done by Bertolotti, M et al., showed that any king of lipid lowering drugs used in age > 65 years was not associated with the increased risk of diabetes [23]. Besides drugs, fibres, phytosterols and red yeast rice has a consistent effect on LDL- cholesterol reduction with good level of evidence [24].

Factors like old age, increased weight, metabolic syndrome and higher blood glucose increase the risk of diabetes and in subjects with the above risk factors, risk-benefit ratio further increases with the use of statin. Improved outcome has been observed in patients undergoing cardiac surgery, therefore guidelines recommend use of statins in patients undergoing coronary artery bypass graft. Although there has been decrease in atrial fibrillation and MI after surgery but poor glycemic control may lead to increase infections and renal complications.

Conclusion

1. Based on epidemiological data from the published literature, clinical trial meta-analyses and Forrest plot analysis of all 14 clinical studies (Figure 1), we have observed that there is increase in risk of development of diabetes with the use of statins. This increased risk appears to be a class effect as it is observed in all the statin subgroups.

2. Considering, the favorable risk-benefit ratio, statin use is recommended in patients with high CVS risk, low CVS risk as well as patients undergoing cardiac surgery.

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