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RESEARCH ARTICLE

ROLE OF STATINS IN DEVELOPING DIABETES MELLITUS

[1]Megha J. R., [1*]Prof. (Dr.) Keerthi G S Nair, [2]Dr. Amal A., and [3]Prof. Dr. Shaiju S. Dharan

[1]Pharm D intern Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences; [2]Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences; [3]Ass. Prof. Dept of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences; [4]Principal, Ezhuthachan College of Pharmaceutical Sciences

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Corresponding author:
Prof. (Dr.) Keerthi G S Nair

ABSTRACT

Background: Diabetes is thought to carry the same risk as coronary heart disease.The higher chance of cardiac mortality and incident coronary heart disease (CHD) development are especially concerning in case of diabetes. The usefulness of statins in primary and secondary prevention of cardiovascular disease (CVD), including among people with type 2 diabetes, is well established. Across all cardiovascular risk groups, there is compelling evidence that statins reduce major vascular events. While statin therapy lowers the risk of cardiovascular disease, there is debate regarding its link to the onset of diabetes. Trials of statin therapy have provided conflicting results regarding statin use and type 2 diabetes (T2DM). ***Methods:*** Previously published articles relating to the topic Statins and Diabetes mellitus have been collected and reviewed. ***Observations:*** Using statins is linked to a higher risk of type 2 diabetes. Using statins is linked to a higher risk of type 2 diabetes (T2DM), which rises with continued usage and higher baseline BMI values. The ongoing researches regarding Statins and Diabetes development will certainly create an alarming sign among the physicians.

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INTRODUCTION

Globally, cardiovascular diseases (CVD) constitute a major source of morbidity and the main cause of early death. As part of the global risk management strategy for CVD prevention, decreasing high blood cholesterol, a risk factor for CVD events, is advised. Statins are frequently used as the first-choice lipid-lowering medicine following health behaviorchanges [(1)]. The first statin to be licensed in the United States was lovastatin in 1987; further approved drugs included fluvastatin in 1994, atorvastatin in 1997, pravastatin and simvastatin in 1991, rosuvastatin in 2003, and Pitavastatin in 2009. Statins inhibit 3-hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase, an intracellular enzyme catalysing the conversion of HMG-CoA to mevalonate during the rate-determined step of cholesterol metabolism. Statin side effects do exist, though, including the increased risk of T2DM and hyperglycemia [(1).] Consequently, the US FDA changed the safety label for statins in 2012, stating that statins raise the concentrations of fasting glucose and glycosylated hemoglobin A1c(HbA1c)[(1).] A number of mechanisms, mainly connected to elevated insulin resistance or decreased insulin production, have been postulated to explain the statin-associated diabetes risk. Due to their pleiotropic properties, lipophilic statins may have adverse metabolic consequences, such as decreased insulin secretion and increased insulin resistance [(3)]. The overwhelming body of research indicates that taking statins increases the chance of developing new-onset diabetes mellitus, however the exact nature of this effect varies across studies due to discrepancies between observational and randomized controlled trials [(3).]Higher doses of statins and high-intensity statin therapy typically carry a higher risk. Prediabetes, genetics, central obesity, dyslipidemia, hypertension, lifestyle, and other drugs—most notably glucocorticoids—are among the several other factors that may play a role[(4).] Hb A1c is somewhat elevated in persons with type 2 diabetes mellitus who take statins; this impact may be more pronounced with atorvastatin than with other statins.

Nonetheless, statins' advantages in preventing atherosclerotic cardiovascular disease exceed their disadvantages in terms of glycemic control [5].

EVIDENCES FROM CLINICAL TRIALS

Largescale, randomised controlled clinical trials conducted recently have suggested that lipophilic statins may elevate the incidence of diabetes with a new onset [6]. In the HPS (Heart Protection Study), diabetes struck 335 participants on simvastatin and 293 participants taking a placebo (hazard ratio: 1.15, 95% confidence interval [CI]: 0.98 to 1.35, p 0.10). The atorvastatin group in the AngloScandinavian Cardiac Outcomes Trial (ASCOT) had a 1.15 (95% CI: 0.91 to 1.44) hazard ratio for diabetes development [6] The treatment group and the placebo group did not differ statistically in either study; nevertheless, there was a trend in both directions toward a rise in newly diagnosed diabetes. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention TrialEvaluatingRosuvastatin), trial evaluated rosuvastatin as a preventive intervention, and the results showed that 20 mg of rosuvastatin increased the rate of new diabetes onset (3.0% versus 2.4%, p=0.01). Randomized controlled trial meta - analysis suggested possible variations between statins, with Atorvastatin, Rosuvastatin, and Simvastatin collectively exhibiting a significant increase in risk (Risk ratio: 1.14; 95% Cl:1.02 to 1.28) versus placebo and Pravastatin exhibiting a trend towards a reduction in risk (risk ratio: o.84; 95% Cl: 0.86 to 1.49) (7). A meta - analysis of six studies, including WOSCOPS and JUPITER, was conducted by Rajpahak et*al.* WOSCOPS inclusion raised the risk of new onset T2DM by 6% (P = NS) while its exclusion increased the risk by 13% (P = .008)[7].

Another meta - analysis of the same six studies plus an additional seven for a total of 13 was conducted by *Sattar et al.* The outcomes of each trial varied greatly (Table 1) 5 in 4 trials, the control group had a greater incidence of new onset diabetes than the statin group, but in the other nine, the statin group had a higher incidence.None of the results were statistically significant when taken as a whole, but when statins were added, the odds ratio for new onset diabetes was 1.09, which was significant (95% CI 1.02-1,17)[7,8]

STATINS AND DIABETES

RESULTS

A total of 161,808 postmenopausal women without diabetes mellitus were recruited by the Women's Health Initiative; 153,840 of these women had sufficient data for post hoc analysis[9]. A 71% increased incidence of new onset diabetes mellitus was linked to statin medication. Even after controlling for age, BMI, family history of diabetes, and other factors, statin users continued to have a 48% greater risk. A database containing over 30,000 patients who had undergone percutaneous intervention for acute coronary syndromes was used by *Lin et al*.[10] The study employed propensity score matching (n = 9,043 in each group) to assess the impact of statin use versus non usage on diabetes with a recent start. Statin use was actually linked to a reduced risk of diabetes in the unmatched cohort.

Table 1. Trial of statins and risk of diabetes with statin use

TRIAL AND STATIN	RISK OF DIABETES WITH STATIN USE
Trial of atorvastatin	
ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm)	Higher
Trials of simvastatin	
HPS (Heart Protection Study)	Higher
4S (Scandinavian Simvastatin Survival Study)	Higher
Trials of rosuvastatin	
Jupiter (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin)	Higher
Corona (Controlled Rosuvastatin Multinational Trial in Heart Failure)	Higher
Gissi HF (Gruppo Italiano per lo Studio dellaSopravvivenzanell'InfartoMiocardico–Heart Failure)	Higher
Trials of pravastatin	
Woscops (West of Scotland Coronary Prevention Study	Lower
Lipid (Long-Term Intervention with Pravastatin in Ischaemic Disease)	Lower
Mega (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese)	Higher
Allhat-Llt (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)	Higher
Gissi Prevenzione (Gruppo Italiano per lo Studio dellaSopravvivenzanell'InfartoMiocardico–Prevenzione)	Lower
PROSPER (Prospective Study of Pravastatin in the Elderly at Risk)	Higher
Trial of lovastatin	
AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)	Lower

Nonetheless, in the matched sample, statin users had a greater risk of developing new onset diabetes compared to non - users (adjusted hazard ratio 1.27, 95% CI 1.14≤.001)[10,11]. Depending on the statin the patients were taking, the hazard ratios changed; all of them were statistically significant, with the exception of lovastatin, where the risk was lower in lovastatin users than in those who were not taking any statins at all. The subsequent were the risk ratios:

- Lovastatin 0.87
- Atorvastatin 1.30
- Fluvastatin 1.38
- Rosuvastatin 1.42
- Pravastatin 1.71.

A meta-analysis of 15 observational studies and 8 randomized controlled trials was conducted by *Engeda et al*. (2008). They demonstrated that the risk was higher in observational studies (relative risk 1.55, 95% CI 1.39–1.74) than in randomized controlled trials (relative risk 1.11, 95% CI 1.00–1.22) and discovered a correlation between the use of statins and new-onset diabetes mellitus. [11]In conclusion, the majority of the data point to a link between statin use and a higher risk of developing diabetes mellitus at the outset of fresh onset; however, the strength of this link differed throughout research, possibly due to the distinctions between observational and randomized controlled trials. [11]

HOW STATINS CAUSES DIABETES

The idea that statins may induce diabetes by modifying glucose homeostasis through reduced insulin sensitivity and decreased insulin production is supported by certain experimental research. The primary signal for insulin release is glucose. Glucose transporters 2 (GLUT2) are responsible for delivering glucose into beta cells. The enzyme glucosekinase phosphorylates glucose to glucose-6-phosphate inside beta cells. ATP which is generated after additional metabolic processes, blocks potassium channels that are sensitive to ATP. As a result of the membrane depolarization, that follows, calcium channels and causes insulin containing granules to be exocytosed. Lipophilic statins, such as Simvastatin, have been shown to block L type Ca2+ channels in beta cells, hence inhibiting glucose induced cystolic Ca2+ signaling induced insulin production. Notably, the inhibitory potencies of these statins are correlated with their lipophilicities. [12]

Numerous metabolites, including isoprenoid, farnesyl pyrophosphate, geranyl pyrophosphate, and ubiquinone (Coenzyme Q10 [CoQ10]), are typically formed during the process of synthesising cholesterol from acetyl CoA. Statins have the ability to lower these metabolites, which could negatively impact insulin action or secretion[12].For instance, it has been demonstrated that statins lower the levels of CoQ10, an element of the electron transport chain that is necessary for the synthesis of ATP. Decreases in CoQ10 can cause ATP synthesis to be delayed, which in turn can reduce insulin release. Moreover, downregulation of GLUT4 in adipocytes has been linked to statin-induced suppression of isoprenoid production. In skeletal muscles and adipocytes, insulin induced glucose uptake is mediated by GLUT4.It has been demonstrated that simvastatin and atorvastatin reduce GLUT4 expression in adipocytes, which may lead to poor glucose tolerance [12].

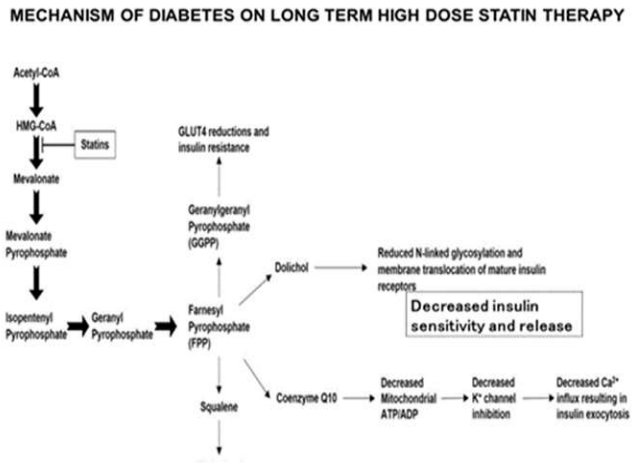

Fig 1. Mechanism of Diabetes in Long Term High Dose Statin Therapy

Adipocytes release the anti-inflammatory and insulin-sensitizing cytokine adiponectin. It has been demonstrated that simvastatin and rosuvastatin lower insulin sensitivity and plasma adiponectin levels, whereas pravastatin raises both. The WOSCOP study's finding of protection against NOD may be attributable to this pravastatin effect. Diabetes etiology has been associated with mitochondrial dysfunction in beta cells, skeletal muscles, adipocytes, and muscles in general[13].

Given that statins are known to induce mitochondrial dysfunction in skeletal muscles, it is conceivable that a related mechanism underlies their tendency to induce diabetes. Furthermore, myalgia and fatigue brought on by statins may make it harder to exercise and exacerbate sarcopenia, which is linked to type 2 diabetes and glucose intolerance.Thus, statin-associated glycemic control impairment and risk of non-Obesity diabetes (NOD) may result from many causes. Additional research is required to validate these conjectures. [13]

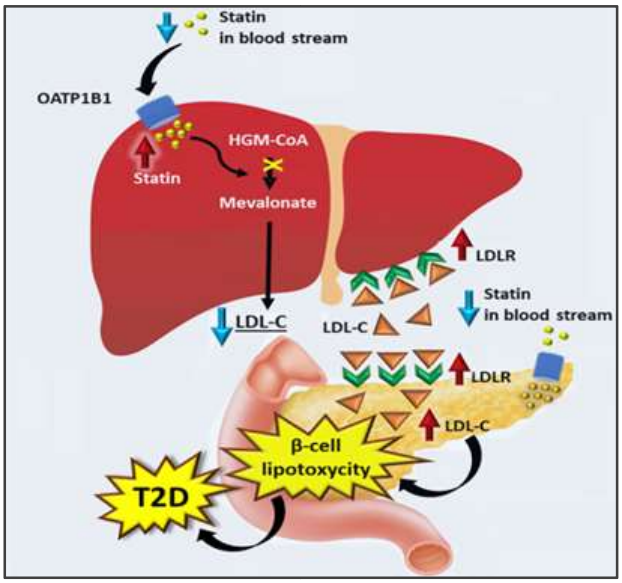

Fig. 2. Mechanism by which Statins increase the risk of Type 2 DM

IMPACT OF STATIN MEDICATION ON GLUCOSE REGULATION IN INDIVIDUALS WITH PRIOR T2DM DIAGNOSIS

In their meta-analysis, *Zhou et al.* examined the impact of statin therapy on glucose regulation in 3,232 individuals with a prior diagnosis of type 2 diabetes from 26 relevant trials. The researchers discovered that these individuals' glycaemic control (HbA1c, fasting glucose) was unaffected by statin medication. *Cui et al.* had different findings. They examined HbA1c variations in 23 trials, involving 2,707 patients with prior T2D diagnoses, and discovered a modest but noteworthy rise in HbA1c when statins were contrasted with placebo. While moderate-intensity pitavastatin improved glycaemic management, high-intensity atorvastatin made it worse [21,22,23]. In nine trials, *Erqou et al.* analysed data from 9 696 patients (4716 controls, 4 980 on statins). After an average follow-up of 3.6 years, the mean HbA1c of the patients assigned to statin treatment was significantly but moderately higher by 0.12% compared to the control group. A meta-analysis of HbA1c concentrations based on 67 studies including more than 25,000 T2D patients was carried out by *Alvarez Jiménez et al*[21]. HbA1c was raised by 0.21% by statins. *Mansi et al.* looked at 83,022 statin users and non-users to see if there was a relationship between the start of statin therapy and the development of diabetes[18]. The researchers discovered that people on statins were more likely to require more glucose-lowering medicine, develop severe hyperglycemia, and begin insulin therapy. Compared to non-users, statin users were linked to a higher risk of diabetes development while using

high-intensity LDL-C reducing medicine. Significant information regarding the impact of statin therapy on patients' glycaemic control was provided by this study [18]. In conclusion, statins made hyperglycemia worse in people with prior T2D diagnosis, while they only slightly raised HbA1c. Insulin treatment initiation and T2D progression were more likely among statin users [20].

GENETIC VARIANT'S EFFECTS ON THE FUNCTION OF STATINS AND THE RISK OF T2DM

The solute carrier organic anion transporter family member 1B1 gene (SLCO1B1), 3-Hydroxy-3-Methylglutaryl-CoA Reductase (HMGCR), and Low-Density Lipoprotein Receptor (LDLR) are the three genes whose genetic variations affect statin function. A member of the organic anion transported family exclusive to the liver is encoded by the SLCO1B1 gene. The liver exhibits high levels of expression for the encoded protein known as organic-anion transporting polypeptide 1B1 (OATP1B1). Statins and a number of other endogenous metabolites are transported into the liver by OATP1B1.SLCO1B1 gene genetic variations are linked to decreased transporter function. A significant risk factor for statin-induced myopathy is the SLCO1B1 rs4363657 variation. There is no discernible correlation between SLCO1B1 rs4149056-C and glucose concentrations, insulin sensitivity, insulin secretion, or the incidence of type 2 diabetes [22].

The enzyme that limits the rate at which cholesterol is synthesized is HMG-CoA reductase. It is controlled by a negative feedback system that is mediated by mevalonate-derived sterols and non-sterol metabolites. The HMG-CoA reductase enzyme, which inhibits the synthesis of mevalonate, cholesterol, and its byproducts, is inhibited by statins. The significance of the HMG-CoA gene as a risk factor for type 2 diabetes has been elucidated by multiple investigations. There is debate over the contribution of weight gain and the effects of HMGCR polymorphisms as causative factors for the development of T2DM. It's crucial to keep in mind that gaining weight raises insulin resistance without directly influencing insulin secretion. When decreased insulin sensitivity cannot be compensated for by increased insulin secretion from pancreatic b-cells, insulin secretion decreases. Overall, the HMGCR rs17238484-G allele was found to increase the risk of type 2 diabetes by 2%, body weight by 0·30 kg, waist circumference by 0·32 cm, glucose concentration by 0.2%, and plasma insulin concentration by 1.6%. Since these modifications were minimal, additional research is required to validate the initial findings [22].

Pathogenic mutations in the LDLR gene, either homozygous or heterozygous, can cause familial hypercholesterolemia. These mutations cause the expression of LDL receptors or the cell uptake of LDL-C. *Fall et al.* found a strong correlation between a lower risk of type 2 diabetes and genetically elevated levels of circulating LDL-C. [21] Patients with familial hypercholesterolemia are less likely to develop diabetes, according to two further studies. In conclusion, growing data indicates that a higher LDL-C concentration is inversely linked to a lower risk of type 2 diabetes, but there isn't enough proof to conclude that the relationship is causal[20].

CLINICAL RAMIFICATIONS OF USING STATINS: Statins successfully reduce LDL-C concentrations and the risk of CVD events (coronary deaths, coronary revascularizations, myocardial infarctions, and strokes), according to a number of randomised trials. According to estimates, if 10,000 people receive an effective statin treatment for around five years, approximately 1,000 patients (10%) who are at high risk of heart attacks and strokes (secondary prevention) and 500 patients (5%) who are at lesser risk (primary prevention) will not experience a significant cardiovascular disease event. Hydrophilic statins (atorvastin, lovastatin, fluvastatin, simvastatin) and hydrophilic statins (rosuvastatin, pravastatin) do not significantly differ in terms of cardiovascular outcomes. The primary side effects of statin therapy are hemorrhagic strokes, incident T2D, and myopathy (pain or weakening in the muscles)[19]. There is strong evidence from a number of trials that statin therapy prevents CVD more effectively than it may harm people by raising their risk of T2D. Therefore, there is no reason to stop taking statins because of the risk of diabetes. Obesity, blood pressure, total triglycerides, and smoking are some of the risk factors for type 2 diabetes (T2D). As a result, adopting a healthy lifestyle also helps to avoid T2D [20].

CLINICAL ASPECTS TO TAKE INTO ACCOUNT

The following actions may assist the physician in giving their patients the best possible protection against CVD while also preventing NOD

Monitoring: The fasting glucose level and HbA1c should be used to track all patients receiving intensive-dose statin medication on a frequent basis.

Information concerning the risk to the patient: Patients will be more receptive to lifestyle changes and the healthcare professional won't be exposed to future legal issues if they are aware of the potential risk of T2DM associated with statin treatment.

Prescribe only when clearly indicated: There are reports indicating that statins are being prescribed without sufficient proof. They shouldn't be viewed as miracle cures and should only be taken when there is a demonstrated therapeutic benefit.

Begin with small doses: Low doses of medication should be administered initially since intensive-dose therapy entails a higher risk. It is preferable to avoid high dose statins in women and the elderly.

Changes in lifestyle: It is important to emphasize the advantages of consistent exercise and dietary adjustments to patients at every opportunity [15,16].

CONCLUSION

The researches that is now available clearly confirms that statins do raise the risk of T2DM. This suggests that some statins—including atorvastatin, rosuvastatin, and simvastatin—have stronger relationships than others (like pravastatin). While the link's causality remains to be

established, there are indications from experimental research that lend credence to this association. Even though, Apolipoprotein B and LDL cholesterol levels were beneficially reduced, Atorvastatin treatment led to significant increases in glycated haemoglobin and fasting insulin levels, which are indicative of insulin resistance, as well as elevated ambient glycemia in patients with hypercholesterolemia.

Although baseline fasting glucose and other metabolic syndrome characteristics continue to be the best indicators of new-onset T2DM, the usage of high-dose atorvastatin may be somewhat related with an increased risk of the condition. In patients with coronary or cerebrovascular illness, atorvastatin clearly outweighs the risks, even though there is a chance that it will raise the risk of new-onset type 2 diabetes. This warrants close observation. It is evident that while statin potency significantly increased the risk of T2DM in population research, the risk of T2DM in clinical trials has been rather similar across statins. There are still many unsolved questions, but the information that is now available indicates that statins do raise the risk of non-occlusive diabetes. This suggests that some statins—including atorvastatin, rosuvastatin, and simvastatin—have stronger relationships than others (like pravastatin). While the link's causality remains to be established, there are indications from experimental research that lend credence to this association.It is challenging to balance the risk of T2DM against the benefit of preventing adverse cardiovascular events, even if benefits seem to outweigh hazards in people with moderate to high CVD risk. It is debatable if they should be used for primary prevention in populations with low CVD risk. To clarify the situation as it stands right now, certain clinical trials are in progress. Until then, statin users should exercise greater caution and vigilance when using them, carefully weighing the advantages over the hazards.

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