Association Between Statin Therapy and Diabetes Risk

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ABSTRACT

Worldwide, statins are the most commonly used drugs to prevent adverse cardiovascular events. The US Food and Drug Administration (US FDA), in 2012, revised statin drug labels to include information that statins increase fasting serum glucose and glycated hemoglobin levels as they show adverse effects on glucose control among diabetic patients. Statins affect glucose control through several mechanisms, by affecting insulin production and secretion by β-pancreatic cells, insulin resistance, insulin uptake by the muscles and adipocytes and production of adipokines. Data from many randomized controlled trials and observational studies indicate increased risk for the emergence of new-onset diabetes after statin initiation. High-dose statins appear to be more effective in established cardiovascular disease, but at the expense of increased drug side effects. Many studies done on patients with cardiovascular risk factors have shown that statins have diabetogenic potential and the effect varies as per the dosage and type of statin used. Research in this area needs to be explored more. Physicians might still take some precautions to make risk-benefit ratio more favorable for the patients. The objective of this review is to evaluate the mechanism, evidence from various clinical trials and precautions before start of statin therapy. This review is based on published journal articles obtained through MEDLINE full text, PubMed, Science Direct, Pro Quest, SAGE, Google Scholar and Elsevier Clinical Key.

Keywords: Statins, new-onset diabetes, glucose control, insulin resistance, insulin sensitivity

Statins are the most widely prescribed drugs for primary and secondary prevention of cardiovascular diseases, but recent evidence has proven that statins may be responsible for new-onset diabetes. As a result, the Food and Drug Administration (FDA), in 2012, revised statin drug labels to include information that statins have been found to increase glycosylated hemoglobin (HbA1c) and fasting serum glucose levels. There are currently seven types of statins available in the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. All statins are cholesterol-lowering agents with the primary effect of reducing cardiovascular risks. Many studies on various classes of lipid-lowering drugs have demonstrated that lipid altering medications may affect glucose control and insulin sensitivity. Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by increased plasma glucose concentration (hyperglycemia) caused by persistent insulin resistance, and progressive β-cell failure. T2DM and cardiovascular diseases are comorbid with each other. Metformin is the first-line treatment for T2DM patients and statins are prescribed as first choice treatment for T2DM patients with dyslipidemia, because of their low-density lipoprotein cholesterol (LDL-C) lowering effects. The current review aims to discuss the mechanisms of how lipid-lowering therapies affect glucose control and the clinical evidence, which supports the study and measures to avoid statin-induced T2DM. This review is based on the information and data gathered from published journal articles obtained through MEDLINE full text, PubMed, Science Direct, Pro Quest, SAGE, Google Scholar and Elsevier Clinical Key.

MECHANISMS FOR THE DIABETOGENIC EFFECTS OF STATINS

Effect of Statins on Insulin Production and Secretion by Pancreatic β-cells

The potential mechanisms include the effects of statins on hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibition, which plays a key role in synthesizing sterol isoprenoids. Statins reduce glycemic control by blocking the production of several metabolites

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usually produced during cholesterol synthesis in the mevalonate pathway.

Glucose is transported by glucose transporter 2 (GLUT2) into β-cells, in which it is routed to the metabolic pathway after phosphorylation to glucose-6-phospate by glucokinase. The metabolic cascade involves closing of the ATP-dependent potassium channel, cell membrane depolarization and L-type calcium channel-mediated calcium influx, resulting in the secretion of insulin by exocytosis of insulin-containing granules. Glucokinase is inhibited by abundance of plasma cholesterol and is affected by statin-induced inhibition of *de novo* cholesterol synthesis with increased uptake of plasma LDL. Statins have been shown to inhibit this glucose-induced calcium signaling-dependent insulin secretion.

In addition, statins suppress the synthesis of ubiquinone (CoQ10), an essential factor in the mitochondrial electron-transfer system, resulting in inhibition of insulin secretion due to reduced production of ATP. Nakata et al demonstrated that statins decrease the expression of another glucose transporter in adipocytes (GLUT4), resulting in impaired glucose tolerance. Statin inhibition of HMG-CoA reductase suppresses the synthesis of isoprenoids, thus causing downregulation of GLUT4 expression on adipocyte cells, leading to impaired glucose uptake. The diabetogenic effects of statins center on altered secretion of islet β-cell insulin, which affect the function of the β-cells and thus precipitate dysregulation of glucose metabolism. The inhibition of HMG-CoA reductase causes upregulation of LDL receptors for enhanced uptake of LDL-C. The oxidation of LDL-C may incite an inflammatory cascade that compromises the functional (insulin secretion apparatus) and structural integrity of the islet β-cells. Over-production of nitric oxide (NO) by cytokines can cause β-cell destruction via the activation of calpain, a calcium-dependent protease. High-density lipoprotein (HDL) protects β-cells against apoptosis, while LDL has the ability to induce apoptosis, particularly following oxidative modification. The interplay between inflammation, oxidation and apoptosis, triggered by increased abundance of plasma-derived LDL-C due to statin-induced blockade of *de novo* cholesterol synthesis may contribute to the pathogenesis of diabetes during extended statin use. Figure 1 depicts the effect of statins on mevalonate pathway.

Effect of Statins on Adipose Tissue

Adipose tissue is responsible for the secretion of an array of signaling molecules termed as adipokines (leptin, adiponectin, resistin and visfatin). Adipokines could lead to an inflammatory response in the adipose tissue, which could play a role in the development of insulin resistance. A dysfunction of adipokines can be implicated in obesity, type 2 diabetes and the increased risk of cardiovascular disease.

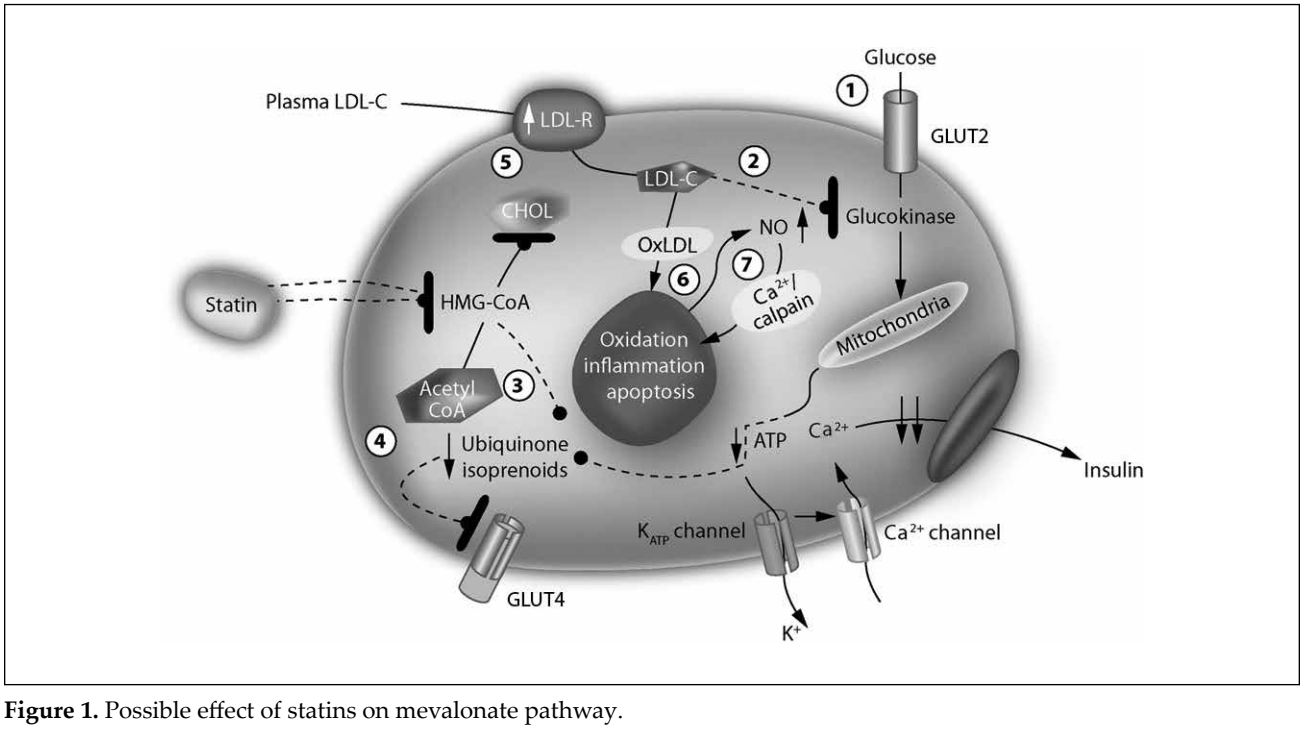

Figure 1. Possible effect of statins on mevalonate pathway.

The adipose tissue contains distinct regions of lipid storage known as lipid rafts and caveolae. Caveolae have integral membrane proteins (Cav-1 and Cav-2). Statins show an inhibitory effect on the caveolae formation through low Cav-1 levels. As adiponectin levels and Cav-1 positively correlate with each other, when statins inhibit the Cav-1 expression, the mechanism of the secretion of adiponectin is also disrupted.

Adipocyte maturation/differentiation is a process all preadipocytes must undergo before they can secrete insulin sensitizing hormones along with GLUT4 translocation and therefore directly affects insulin resistance. An accumulation of undifferentiated adipocytes may lead to increased insulin resistance and the risk of the development of statin-induced diabetes. Macrophages present in the adipose tissue possess several proinflammatory cytokines such as tumor necrosis factor (TNF)-α that inhibit insulin action along with adiponectin production in adipocytes, thus leading to risks of inflammation. Effect of statins on adipose tissue has been summarized in Figure 2.

Effect of Statins on Skeletal Muscle

Several factors are responsible for contributing to statin effect on myopathy:

- Statins reduce LDL-C by altering the mevalonate pathway and thus may result in the impaired mitochondrial oxidative metabolism as well as energy production.
- Adversely affect the ubiquitin-proteasome pathway (UPP) which plays an important role in the structural integrity of the skeletal muscle and is responsible for the degradation and repair of many skeletal muscle proteins.
- Statin-induced apoptosis could also occur via calpain (stimulates programmed cell death), repression of the Birc4 and the activation of proapoptosis gene CFLAR.
- Finally, statins alter Ca^{2+} homeostasis by increasing systolic Ca^{2+}, which might impair sarcoplasmic reticulum calcium cycling.

EVIDENCE FROM CLINICAL TRIALS

Clinical studies have yielded inconclusive results on the association between statin usage and blood sugar. Preclinical and clinical data show the effect of statins on various parameters of glycemic control. Many studies have shown that atorvastatin, rosuvastatin and simvastatin increase both HbA1c and fasting plasma glucose (FPG) levels. A large scale study implicates that pravastatin reduced the rate of new-onset diabetes by 30%. Atorvastatin attenuates adipocyte maturation, resulting in inhibiting isoprenoid synthesis, and impairs glucose tolerance. Simvastatin blocks L-type Ca^{2+} channels, resulting in decreased insulin secretion. Lovastatin was shown to downregulate GLUT4 and upregulate GLUT1, leading to inhibition of insulin-stimulated glucose transport. Further, it has also been indicated that the risk for new-onset diabetes holds probably true for all statins and occurs in a dose-dependent fashion. Table 1 suggests an association between statin therapy and new-onset diabetes.

The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial reported a 25% increase with rosuvastatin 20 mg, over a median follow-up of 1.9 years, compared to placebo. Navarese et al

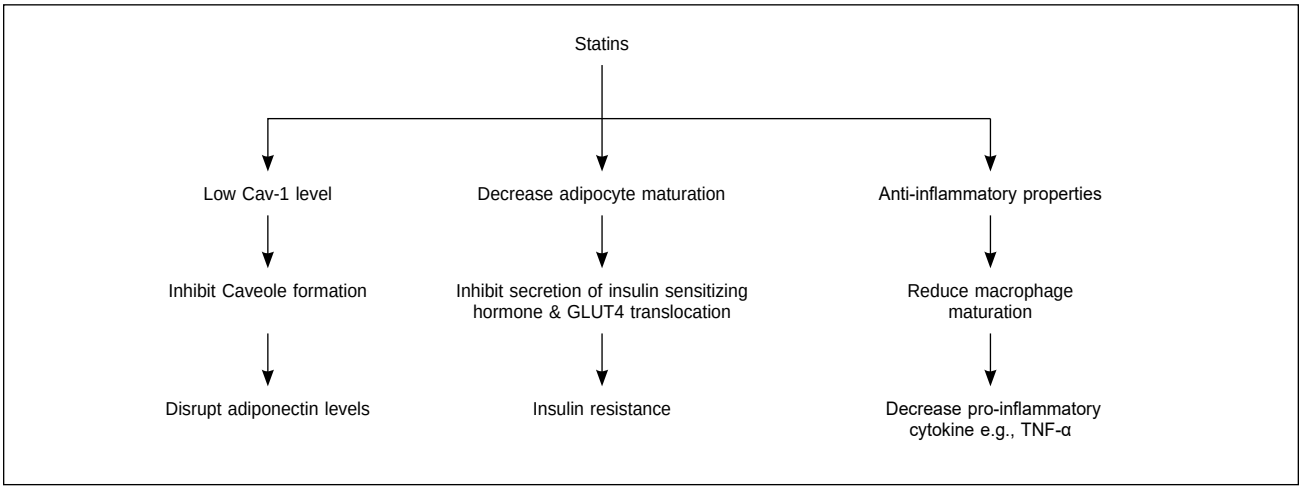

Figure 2. Effect of statins on adipose tissue.

Table 1. Randomized Controlled Trials Evaluating the Effect of Statin Use and Risk of T2DM

Study (year of primary publication)	Comparison vs. placebo	Study population	Event or incident (statin/placebo)	OR (95% CI)
WOSCOPS (2001)	Pravastatin 40 mg	5,974	75/93	0.79 (0.58-1.10)
HPS (2003)	Simvastatin 40 mg	14,573	335/293	1.15 (0.98-1.35)
ALLHAT-LLT (2002)	Pravastatin 40 mg	6,087	238/212	1.15 (0.05-1.41)
LIPID (2003)	Pravastatin 40 mg	6,997	126/138	0.91 (0.71-1.71)
ASCOT-LLA (2003)	Atorvastatin 10 mg	7,773	154/134	1.14 (0.89-1.46)
MEGA (2006)	Pravastatin 10-20 mg	6,086	172/164	1.07 (0.86-1.35)
CORONA (2007)	Rosuvastatin 10 mg	3,534	100/88	1.14 (0.84-1.55)
JUPITER (2008)	Rosuvastatin 20 mg	17,802	270/216	1.26 (1.04-1.51)

found added new-onset diabetes risk of 7% with pravastatin (40 mg), 15% with atorvastatin (80 mg) and 25% with rosuvastatin (20 mg), in a meta-analysis of 17 controlled randomized trials. They accomplished that the diabetes incidence increases differently with the type of statin and doses used.

Ridker et al analyzed the JUPITER trial results in patients with none or minimum one risk factor for developing diabetes (body mass index [BMI] ≥30 kg/m^2, metabolic syndrome or HbA1c ≥6%, impaired fasting sugar) and found that in individuals with one or more risk factors, statin use was associated with a 28% increase in diabetes (1.28, 1.07-1.54, p = 0.01). For those with no major diabetes risk factors, statin allocation was associated with no increase in diabetes (0.99, 0.45-2.21, p = 0.99). Therefore, the patients carrying some diabetes-related risk factors were at increased risk of developing diabetes, and advantages of statin treatment surpassed the diabetes vulnerability, even in those at increased risk of becoming diabetic.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE-IT TIMI) 22 trial, among pravastatin 40 mg treated patients, the HbA1c levels increased by 0.12%, while atorvastatin 80 mg group showed 0.30% rise. Another study comparing glycemic control between diabetic patients receiving atorvastatin 10 mg pravastatin 10 mg or pitavastatin 2 mg/day showed that the blood glucose and HbA1c levels increased only in the atorvastatin-treated patients. Pitavastatin, the newest statin has revealed positive outcome by reducing insulin resistance and effect on glucose metabolism was minimal.

Lipophilic statins (atorvastatin, simvastatin, fluvastatin, pitavastatin and lovastatin) are more likely to cause diabetes as they can easily enter extrahepatic cell membranes like adipocytes, skeletal muscles and β-cells, whereas hydrophilic (pravastatin and rosuvastatin) statins are highly specific to hepatocytes and have minimal chances of entering adipocytes or β-cells.

The diabetogenic effect of statins in women may not be similar to that in men. Culver et al observed that statin use among postmenopausal women participating in the Women's Health Initiative was associated with an increased risk for type 2 diabetes. This effect was observed for all types of statins, thus appearing to be a class effect.

MEASURES TO AVOID STATIN-INDUCED NEW-ONSET DIABETES

Statins' adverse effect on glycemic control needs to be explored more. The physicians, before starting statin therapy, can take some precautions to make risk-benefit ratio more favorable to the patients. They can follow some points which have already been mentioned by Aiman et al.

- Screening for type 2 diabetes (T2DM) before starting statin therapy.
- Since high-dose treatment is associated with higher risk, start therapy with low doses and when clearly indicated, avoid high doses in women and elderly population.
- While simvastatin, rosuvastatin and atorvastatin all increase the risk, pravastatin appears to reduce risk for new-onset diabetes.

- Regular exercise and diet control benefit the patients. They should be stressed regularly. Since insulin resistance has shown association with vitamin D deficiency, addition of vitamin D might improve insulin sensitivity.
- Patients should be informed about the possible risk of diabetes.

Studies prove that T2DM and CVDs are comorbid with each other. Dyslipidemia and insulin resistance are the risk factors for myocardial infarction. A recent review by van Stee et al suggests the combination therapy of metformin and statin to treat T2DM. As statin increases the risk of T2DM particularly in prediabetic subjects, co-treatment with metformin might reduce this risk.

CONCLUSION

The incidence of new-onset diabetes varies among randomized clinical trials. The clinical data suggest that statin therapy is associated with an increased risk for diabetes. Comparisons of the higher and lower dose of statins suggest that there may be a higher risk for incident diabetes at higher doses and may also vary with the type of statins. Furthermore, more potent statins, such as atorvastatin and simvastatin, have been associated with a higher rate of diabetes compared with lower potency statins. Still, efforts are required to explore the relationships between statin therapy and diabetes, both in future clinical trials and preclinical investigations. Since metformin shows beneficial effects on both dyslipidemia and glycemic control and has been shown to reduce CVD risk while statins have an added beneficial effect on CVD risk, combined treatment with both the drugs can be a better option. So, the combination therapy of metformin and statins can reduce the risk of statin-induced diabetes. Still, more studies are required to prove the role of combined metformin-statin treatment.

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IJCP SUTRA 601: 'Common cold' refers to a mild upper respiratory viral illness presenting with sneezing, nasal congestion, nasal discharge, low-grade fever, headache and malaise.

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