

# Statin induced diabetes and its clinical implications

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## ABSTRACT

Statins are one of the most commonly used drugs in the world based on their potential to prevent adverse cardiovascular events. These cholesterol-lowering drugs received a US Food and Drug Administration warning, in February 2012, regarding increased risk of incident diabetes and impaired glycemic control in patients who already have diabetes. The possible association of diabetes with statin therapy has started a wave of discussion in the medical community. A number of meta-analyses conducted in recent years have demonstrated that the association is real although causality has not been proved yet. Individual statins differ with respect to their diabetogenic property; women and elderly persons appear to be at increased risk. Various aspects of statin's adverse effect on glycemic control remain to be explored. As further research in this area continues, physicians might still take some precautions to make risk benefit ratio more favorable for the patients.

**Key words:** Cardiovascular disease, insulin resistance, statins, type 2 diabetes

## INTRODUCTION

*“Then comes the question, how do drugs, hygiene and animal magnetism heal? It may be affirmed that they do not heal, but only relieve suffering temporarily, exchanging one disease for another”.*

-Mary Baker Eddy, US Religious Leader.

Statins are one of the most widely prescribed groups of drugs in the world. Although statins have been shown to be beneficial in primary and secondary prevention of cardiovascular

disease (CVD) in a number of trials, current reports of increased risk of type 2 diabetes with statin use are of concern. As a result of these reports, on February 28, 2012, the Food and Drug Administration added new safety label changes for the statin class of cholesterol-lowering drugs regarding the potential for increased hemoglobin A1c (HbA1c) and fasting plasma glucose. The present review discusses the evidence available from clinical trials and meta-analyses regarding possible diabetogenic effect of statins, probable mechanisms of this association and how these new observations might change clinical approach to statin use.

## EVIDENCE FROM CLINICAL TRIALS

Although there had been reports of impaired glucose tolerance and increased risk of diabetes associated with use of statins, not much attention was paid to this issue until the publication, in 2008, of results of Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), which was a large, randomized, placebo controlled, primary

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prevention trial.<sup>[1]</sup> Increased incidence of diabetes in persons taking rosuvastatin was reported in this trial, which included 17,802 men and women (average age 66 years) who were randomized into two groups: rosuvastatin (20 mg/day) or an inactive placebo drug. This trial was stopped early at 1.9 years when an interim analysis found a 44% lower incidence of adverse vascular events in the rosuvastatin group. There was a 26% higher incidence of diabetes in the rosuvastatin group. The results of JUPITER started a wave of discussion regarding potential risks and benefits of statin therapy.

Before the results of JUPITER were out, the West of Scotland Coronary Prevention Study (WOSCOP) study (2001) had reported a 30% risk reduction for diabetes with the use of pravastatin (40 mg).<sup>[2]</sup> In contrast, the prospective study of pravastatin in the elderly at risk, found a 32% higher incidence of diabetes with pravastatin therapy.<sup>[3]</sup> Furthermore, pravastatin (40 mg) did not reduce the incidence of diabetes in the long-term intervention with pravastatin in ischemic disease trial.<sup>[4]</sup>

## WHAT META-ANALYSES SAY?

In the background of conflicting results of clinical trials, a few meta-analyses conducted in the past 5-6 years help to resolve the issue to some extent if not completely. In a meta-analysis by Coleman *et al.*, statins as a class were not found to be associated with increased risk of new onset type 2 diabetes.<sup>[5]</sup> This meta-analysis included five prospective randomized controlled trials (including WOSCOP) involving 39,791 patients. Authors reported a statistical heterogeneity resulting from pravastatin's tendency toward a reduction in risk and the other statins showing an increased risk. This meta-analysis was carried out before results of JUPITER were published.

In a meta-analysis of five trials, Rajpathak *et al.*, found a 13% increase in diabetes risk with no heterogeneity across trials.<sup>[6]</sup> However, when data from WOSCOP was included, this risk became statistically insignificant and resulted in significant heterogeneity among component studies.

A recent meta-analysis by Sattar *et al.*, included 13 randomized placebo controlled and standard care controlled trials (including JUPITER and WOSCOP) with 91,140 participants.<sup>[7]</sup> This meta-analysis demonstrated a 9% increased risk of incident diabetes with little heterogeneity between trials [Figure 1]. It also found that the risk was greater in elderly patients.

Another meta-analysis by Preiss *et al.*, in 2011 confirms that statins have a diabetogenic effect and further concludes that this diabetogenic effect is dose dependent, with 12% higher risk on intensive-dose statin therapy compared with moderate-dose therapy.<sup>[8]</sup> This meta-analysis included five statin trials with 32,752 participants without diabetes at baseline. One additional patient developed diabetes for every

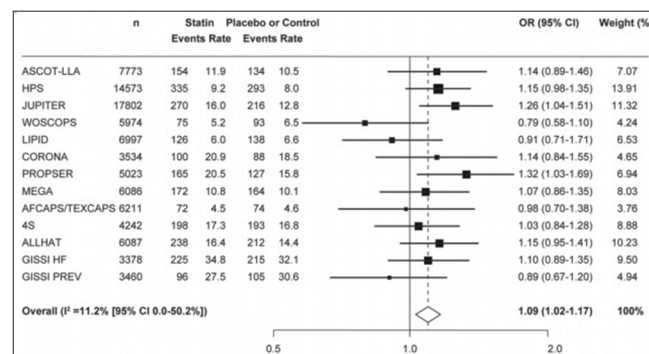
three patients protected from a major cardiovascular event in the intensive-dose group.

Recently, in a *post-hoc* analysis of the JUPITER trial, Ridker *et al.*, concluded that participants with one or more major diabetes risk factor were at higher risk of developing diabetes than were those without a major risk factor; and benefits of statin therapy exceeded the diabetes hazard even in participants at high risk of developing diabetes.<sup>[9]</sup> Most recently, in a meta-analysis of 17 randomized controlled trials, rosuvastatin (20 mg/day), atorvastatin (80 mg/day) and pravastatin (40 mg/day) were found to increase risk of new onset diabetes (NOD) by 25%, 15% and 7%, respectively.<sup>[10]</sup>

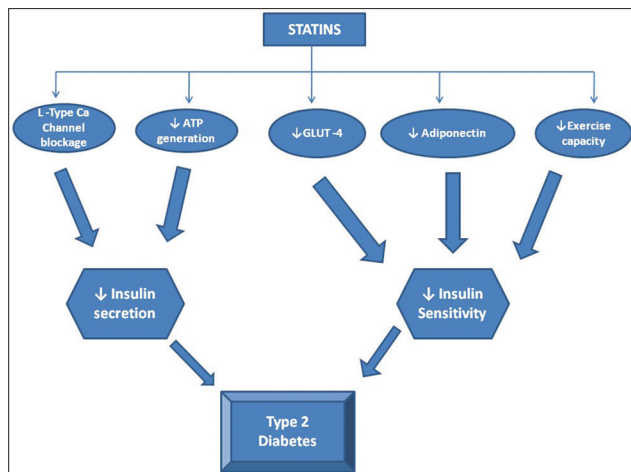
## HOW STATINS MAY CAUSE DIABETES?

Some experimental studies support the hypothesis that statins may cause diabetes by altering glucose homeostasis through both impaired insulin secretion and diminished insulin sensitivity [Figure 2]. Glucose is the most important signal for insulin release. Glucose is transported into the beta cells through glucose transporters 2 (GLUT2). Inside beta cells, glucose is phosphorylated to glucose-6-phosphate by enzyme glucokinase. Following further metabolic steps, adenosine triphosphate (ATP) is produced which closes ATP sensitive potassium channels. Resulting membrane depolarization leads to calcium influx through L-type calcium channels causing exocytosis of insulin containing granules. It has been reported that lipophilic statins (e.g., simvastatin) can inhibit glucose-induced cytosolic Ca<sup>2+</sup> signaling and insulin secretion by blocking L-type Ca<sup>2+</sup> channels in beta-cells and their inhibitory potencies parallel their lipophilicities.<sup>[11]</sup>

During the process of cholesterol synthesis from acetyl CoA, various metabolites such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate and ubiquinone (Coenzyme



**Figure 1:** Association between statin therapy and incident diabetes in 13 major cardiovascular trials (events per 1000 patient-years, weights are from random-effects analysis). "Reprinted from The Lancet, Vol. 375, Sattar *et al.* Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. 735-42. Copyright (2010), with permission from Elsevier"



**Figure 2:** Possible mechanisms of statin induced diabetes

Q10 [CoQ10]) are normally produced. Statins can reduce these metabolites which may affect insulin secretion or action adversely. For example, statins have been shown to reduce levels of CoQ10, which is a component of electron transport chain involved in the process of ATP generation.<sup>[12]</sup> Reduced levels of CoQ10 can result in delayed production of ATP and consequently diminish insulin release. Furthermore, inhibition of isoprenoid biosynthesis by statins has been implicated in downregulation of GLUT4 in adipocytes.<sup>[13]</sup> GLUT4 mediates insulin stimulated uptake of glucose in skeletal muscles and adipocytes. Atorvastatin and simvastatin have been shown to decrease the expression of GLUT4 in adipocytes which may result in impaired glucose tolerance.<sup>[14,15]</sup>

Adiponectin is an insulin sensitizing and anti-inflammatory cytokine released from adipocytes. Rosuvastatin and simvastatin have been shown to decrease plasma adiponectin levels and insulin sensitivity while pravastatin increased both.<sup>[16,17]</sup> This effect of pravastatin may be responsible for the protection against NOD found in the WOSCOP study.

Mitochondrial dysfunction in beta cells,<sup>[18]</sup> skeletal muscles<sup>[19]</sup> and adipocytes<sup>[20]</sup> has been linked with the pathogenesis of diabetes. Since statins are known to cause mitochondrial dysfunction in skeletal muscles,<sup>[21]</sup> it is plausible that similar mechanism is also responsible for their diabetogenic effect. In addition, statin induced myalgia and fatigue may impair exercise capacity and aggravate sarcopenia, which is associated with glucose intolerance and type 2 diabetes.<sup>[22]</sup> Therefore, multiple mechanisms may lead to impairment of glycemic control and risk of NOD with statins. Further studies are needed to confirm these hypotheses.

## DOES SPECIFIC STATIN MATTER?

Atorvastatin, simvastatin, lovastatin, fluvastatin and pitavastatin are relatively lipophilic compounds while

pravastatin and rosuvastatin are relatively hydrophilic.<sup>[23]</sup> It has been hypothesized that lipophilic statins might be more diabetogenic as they can more readily penetrate extrahepatic cell membranes such as beta cells, adipocytes and skeletal muscles while hydrophilic statins (e.g., pravastatin) are more hepatocyte specific and less likely to enter beta cells or adipocytes.<sup>[23]</sup> This hypothesis is also supported by a recent meta-analysis in which pravastatin was found to improve insulin sensitivity while simvastatin worsened the same.<sup>[24]</sup> Although, this hypothesis explains the results of WOSCOP, the risk of NOD with rosuvastatin (as in JUPITER) cannot be explained. Moreover, meta-analysis by Sattar *et al.* failed to find any difference between lipophilic and hydrophilic statins.<sup>[7]</sup>

## IS THERE A GENDER BIAS?

The diabetogenic effect of statins in women may not be similar to that in men. It is worth noting that the WOSCOP study was an all-male study. In other trials discussed earlier, 60-85% of participants were male. In a sex based meta-analysis, statins were reported to have no benefit on stroke and all-cause mortality in women.<sup>[25]</sup> Moreover, statin use among postmenopausal women participating in the Women's Health Initiative was associated with an increased risk for type 2 diabetes (adjusted hazard ratio: 1.48). This effect was observed for all types of statins appearing to be a class effect.<sup>[26]</sup> Future trials evaluating association of statins with incident diabetes should incorporate female participants in adequate numbers.

## A PHYSICIAN'S DILEMMA

Association of statin use with NOD presents a dilemma for the physician due to many reasons. First, type 2 diabetes is a coronary heart disease risk equivalent; second, dyslipidemia is a characteristic feature of diabetes; third, persons at risk for CVD (including dyslipidemic persons) may be prediabetic and finally, risk factors for diabetes and CVD are overlapping. Risk of NOD may thus be feared to offset, to some extent, the benefits of favorable lipid profile on adverse cardiovascular events.

The association of statins with NOD becomes more disturbing in a time when the concept of "MacStatin" (where a statin packet is supposed to be sprinkled onto a Quarter Pounder or in a milkshake) is being promoted.<sup>[27]</sup> Medical community as well as patients might get a false sense of protection and consequently ignore the lifestyle modifications. Pharmaceutical industry also plays a role in projecting statins as magic bullets and it is claimed by some that statins should be "put in the water." Even patients are themselves asking their physician for a statin prescription. A recent study found that direct to customer advertising leads to over diagnosis of high cholesterol

and over prescription of statins to those group of patients where the risks of such therapy may outweigh potential benefits.<sup>[28]</sup>

## CLINICAL CONSIDERATIONS

As we eagerly wait for the results of trials addressing this question more directly, some steps which may help the physician to provide maximum protection from CVD to their patients, at the same time avoiding NOD are as follows.

### Prescribe only when clearly indicated

Reports suggest that statins are being prescribed without good evidence.<sup>[29]</sup> They should be used based on clear therapeutic rationale and not considered to be magic bullets.

### Start with low doses

Since intensive-dose therapy carries higher risk, treatment should be started with low doses. High dose statins are better avoided in women and elderly.

### Choice of individual statin

Although not proven, pravastatin appears to reduce risk for NOD, while atorvastatin, rosuvastatin and simvastatin all significantly increase the risk.

### Lifestyle modifications

Benefits of regular exercise and dietary modifications should be stressed at every contact with the patient.

### Patient information about the risk

It will be wise to inform patients about the possible risk of NOD with statin use since it will make them more compliant with lifestyle modifications and at the same time prevent the health care provider from any legal disputes later.

### Screening of patients

Before starting statin therapy, screening for type 2 diabetes may be considered.

### Monitoring

All patients on intensive-dose statin therapy should be regularly monitored using fasting glucose level and HbA1c.

### Vitamin D supplementation

Vitamin D deficiency has been linked with insulin resistance<sup>[30]</sup> and supplementation of vitamin D has been shown to improve insulin sensitivity.<sup>[31]</sup> Patients on statin therapy may be screened for vitamin D deficiency and treated accordingly.

## FUTURE RESEARCH DIRECTION

A lot of research is currently going on to elucidate mechanisms of statin induced diabetes at the molecular level. In addition, the

Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (J-PREDICT) which was started in 2006, is expected to be completed in 2015.<sup>[32]</sup> The primary outcome measure of this trial is incidence of type 2 diabetes in a population of impaired glucose tolerance. This is the first phase 4 trial to evaluate the effect of a statin on the onset of diabetes as the primary end point. Hopefully, J-PREDICT results will provide useful insights about this controversial topic. Another area of investigation is whether microvascular and macrovascular complications of statin induced diabetes are same as that of non-statin - induced diabetes. Follow-up of participants of trials such as JUPITER might help to provide the answer.

## CONCLUSION

Although a number of questions remain unanswered, the available evidence supports that statins do increase the chances of NOD. In this regard some statins appear to be more strongly related (e.g., simvastatin, rosuvastatin and atorvastatin) than others (e.g., pravastatin). Although causality of this association has not been proved, there are evidences from experimental studies that make this association plausible. It is difficult to weigh benefit; in terms of prevention of adverse cardiovascular events, versus risk of NOD although benefits appear to outweigh risks in moderate to high CVD risk population. Their use in low CVD risk population for primary prevention is controversial. Some clinical trials are underway to make the current picture more clear. Until that time, clinicians using statins should be more cautious and vigilant regarding their use and carefully balance benefits with risks.

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