Statin-Associated Diabetes Mellitus: Review and Clinical Guide

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Abstract: A small but significant link between new-onset diabetes mellitus (NOD) and statin therapy was noted with rosuvastatin users in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin study. Since then multiple analyses have further confirmed this association, with most studies demonstrating a modest increase in NOD with statin therapy, especially among individuals with risk factors for developing diabetes mellitus. More recent observational analyses suggest a stronger correlation between statin use and NOD, however. A definitive mechanism confirming causation between statins and glucose impairment remains elusive, but many have been proposed. Although considered a class effect by the US Food and Drug Administration, most data indicate NOD is dependent upon the dose and potency of the statin, with certain agents appearing to be less diabetogenic.

The consensus is that the benefits of statin therapy far outweigh the risk of NOD, especially among patients with high cardiovascular risk. Nonetheless, more studies are needed to better understand this association and long-term clinical implications. In the meantime, we provide clinicians with a practical guide to assist with clinical decision making when prescribing statin therapy. Overall, this article serves to provide the primary care physician with a timely review of the most clinically relevant data regarding statins and NOD, with hopes to ultimately optimize statin prescribing and limit any potential drug-induced glucose impairment.

Key Words: cardiovascular disease, diabetes mellitus, insulin resistance, statins, type 2 diabetes mellitus

Use of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) to lower low-density lipoprotein-cholesterol (LDL-C) and reducing cardiovascular (CV) events is nearing the 30-year mark. The agents have an acceptable safety profile and are the cornerstone for treating most types of dyslipidemia. The notable finding of higher rates of new-onset diabetes mellitus (NOD) among rosuvastatin users, with the 2008 publication of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, prompted a flurry of subsequent analyses mostly supporting a small association between statins and type 2 diabetes mellitus (DM). As such, the US Food and Drug Administration and the European Medicines Agency each provided statements in 2012 indicating an association with statin therapy and reports of increased hemoglobin A1c (HbA1c) and fasting serum glucose, and an increased risk of NOD in patients already at risk for DM, respectively. Both agencies emphasized the risk–benefit ratio highly favoring statin use.

The association between rosuvastatin and NOD perplexed many in the medical community. Prior data from smaller studies examining statins and glucose impairment produced mixed results. Furthermore, an analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) concluded that statins may even protect against DM, although this was later refuted.

Key Points
- Findings from randomized controlled trials and observational studies have linked statin use with insulin resistance and new-onset type 2 diabetes mellitus.
- Although considered a class effect by the US Food and Drug Administration, data indicate that glycemic changes differ among statins and are dose and potency dependent.
- Practitioners should screen patients before prescribing statin therapy, especially patients who are at risk for type 2 diabetes mellitus.
- Numerous clinical considerations may be used to minimize glucose impairment with statin therapy.
A growing body of evidence, including newer observational analyses, suggests that the link between statins and NOD may be stronger than initially believed. This article reviews the available data regarding this association and provides clinical guidance for practitioners to minimize potential risk.

Large Randomized Controlled Trials
The JUPITER study involved 17,802 individuals (11,001 men aged 50 years and older, 6801 women aged 60 years and older) with C-reactive protein ≥2 mg/L and LDL-C <130 mg/dL, randomized to rosuvastatin therapy (20 mg/day) or placebo. After 1.9 years, an interim analysis revealed an increase in the incidence of physician-reported DM among the rosuvastatin group compared with controls (odds ratio [OR] 1.26, 95% confidence interval [CI] 1.04–1.51) despite a lack of difference observed between groups for fasting glucose or newly diagnosed glycosuria. A significant but small increase in glycated hemoglobin, however, was found among the rosuvastatin group compared with placebo (5.9% vs 5.8%; P = 0.001). Furthermore, a subgroup analysis revealed a higher incidence of physician-reported DM in women treated with rosuvastatin versus placebo compared with men; however, the rosuvastatin group had a lower risk of myocardial infarction (MI), stroke, and death from any cause. In a post hoc analysis of JUPITER, investigators determined that participants with one or more risk factors for DM were at higher risk of developing DM than those without a major risk factor.10

In contrast to JUPITER, WOSCOPS reported that statin therapy significantly reduced DM occurrence among initial non-DM participants (hazard ratio [HR] 0.70, 95% CI 0.5–0.98; P = 0.036). WOSCOPS randomized 6595 men aged 45 to 64 years with hyperlipidemia and no history of MI to pravastatin (40 mg/day) or placebo. The investigators who reported the inverse association between pravastatin use and DM incidence applied nonstandardized criteria for diagnosing DM and later statin trials that included both men and women did not corroborate this protective effect.11,12

Other major pravastatin trials provide mixed results. In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, pravastatin (40 mg/day) did not have an effect on NOD during follow-up compared with placebo (4.0% vs 4.5% respectively; P = 0.32). This trial involved 9014 men and women between the ages of 31 and 75 years who had a history of MI or hospitalization for unstable angina.13 In contrast, investigators reported a 32% higher incidence of DM for those taking pravastatin (40 mg/day) compared with controls in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial (OR 1.32, 95% CI 1.03–1.69).14 The participants in this study included both older men and women between the ages of 70 and 82 years who had either preexisting vascular disease or were at increased risk for vascular disease from factors such as smoking, hypertension, or DM.

Short-Duration Studies
Two small short-term studies reported an association between statin use and glucose metabolism. First, Kostapanos et al evaluated 72 hyperlipidemic patients with impaired fasting glucose receiving daily rosuvastatin therapy (10 mg, n = 24; 20 mg, n = 25; 40 mg, n = 23).15 After 12 weeks, rosuvastatin was associated with a dose-dependent increase in insulin resistance; however, the relatively small sample and the potential for unmeasured confounding factors remain a concern for this retrospective, observational, uncontrolled study. The second, a single-blind, placebo-controlled parallel study involved 213 patients with hypercholesterolemia randomized to placebo (n = 44) or daily atorvastatin (10 mg, n = 42; 20 mg, n = 44; 40 mg, n = 43; 80 mg, n = 40).16 During a 2-month treatment period, the atorvastatin group showed significant increases compared with placebo in fasting insulin and glycated hemoglobin levels, which is consistent with insulin resistance and increased ambient glycemia.

Meta-Analytic Studies
Across 6 years, several meta-analytic studies have been performed in an attempt to resolve the inconsistencies surrounding statin use and NOD. Before the JUPITER trial, a meta-analytic study of 5 prospective randomized controlled trials (RCTs; n = 39,791), which included WOSCOPS, indicated the use of a statin did not significantly influence a patient’s risk of developing DM (relative risk 1.03, 95% CI 0.89–1.19).17

One year later, a meta-analysis of six primary and secondary prevention trials (WOSCOPS, LIPID trial, Heart Protection Study, the [ASCOT], JUPITER, and Controlled Rosuvastatin Multinational Study in Heart Failure [CORONA] trial; n = 57,593) did not indicate a significant risk of DM. When data from WOSCOPS were removed from the analysis, however, a small increase in DM risk was noted (relative risk 1.13, 95% CI 1.03–1.23).18

In 2010, a meta-analysis of 13 placebo or standard care RCT statin trials was performed. Of the 91,140 participants, 2226 (2.44%) receiving statins developed DM compared with 2052 (2.25%) receiving placebo over an average of 4 years.8 Overall, statin therapy was associated with a 9% increased risk for incident DM (OR 1.09, 95% CI 1.02–1.17), with a stronger risk among older adults. Body mass index (BMI) and efficacy of the statin on lipid values did not alter the findings. The risk of incident DM was lower when statins were being used for primary prevention compared with those for secondary prevention. Trials with the highest occurrence of DM included participants known to be at high risk for DM (eg, heart failure, MI within the last 6 months, elderly adult, or at high risk of CV disease). The authors concluded that treating 255 patients with statin therapy for 4 years would result in 1 additional case of DM. The Figure provides the association between different statins and the development of DM in the 13 selected major CV RCTs.8

The following year, Preiss et al wanted to confirm not only the diabetogenic effect of statins but also whether this effect
was dose dependent in a meta-analysis of 5 high-dose trials among 32,752 participants without DM at baseline. After approximately 4.9 years, participants receiving intensive statin therapy had a higher risk of developing DM than those receiving moderate therapy (OR 1.12, 95% CI 1.04–1.22). Results indicated 4.42% on intensive statin therapy developed NOD compared with 3.97% on moderate-dose therapy. Intensive statin therapy, however, also was associated with fewer CV events (OR 0.84, 95% CI 0.75–0.94).

In 2013, a comprehensive study of 17 RCTs (n = 113,394) was undertaken to compare either statin therapy with placebo or high-dose versus moderate-dose therapy. The results of the meta-analysis showed that rosuvastatin (20 mg/day), atorvastatin (80 mg/day), and pravastatin (40 mg/day) increased the risk of NOD by 25%, 15%, and 7%, respectively. The investigators found a gradient for the risk for NOD across different agents and doses of statin therapy.

Cohort Studies

An increased risk of NOD also was found in a retrospective cohort study among patients (n = 1,235,671) treated with statins compared with nonstatin users. Statin use was associated with an increased risk of NOD (HR 1.18, 95% CI 1.15–1.22). Overall, there were statistically significant dose and duration effects for all statins (eg, rosuvastatin, atorvastatin, simvastatin) except fluvastatin, which only showed a duration effect.

A significant increase of NOD also was reported in a prospective population-based cohort study (8749 non-DM participants, 45–73 years old) with a 5.9-year follow-up. After adjustment of confounding factors, statin use was associated with a 46% increased risk of NOD (adjusted HR 1.46, 95% CI 1.33–1.74) and worsening hyperglycemia. Similarly, in the Women’s Health Initiative (WHI), statin therapy was associated with a 48% increase in the risk of self-reported DM after 3 years among postmenopausal women (HR 1.48; 95% CI 1.38–1.59).

In another retrospective cohort study, investigators examined the risk of NOD and DM complications with statin use in a primary prevention Tricare (formerly known as the Civilian Health and Medical Program of the Uniformed Services) population. Patients without severe comorbidities were included and classified according to statin use (n = 3351) or nonuse (n = 3351). Matching study participants on a propensity score, statin use was found to be associated with a significant increase in NOD (OR 1.87, 95% CI 1.67–2.01), DM complications (OR
2.50, 95% CI 1.88–3.32), and overweight/obesity (OR 1.14, 95% CI 1.04–1.25). Although the increased risk of DM with statins has been well described in several analyses, this was the first study to document the increased risk of DM complications among statin users.

Populations Possibly More Greatly Affected

Certain populations, particularly those with multiple features of metabolic syndrome, may be more prone to developing NOD with statin use: existing risk factors for DM (BMI >30, positive for hypertension, triglycerides >150 mg/dL, fasting blood glucose >100 mg/dL), women, older adults, Asian ethnicity, extended duration of statin use, those with a family history of DM. Waters et al analyzed three large statin RCTs and found that in each, fasting blood glucose, BMI, hypertension, and fasting triglycerides were independent risk factors for developing NOD with statin use. It was further determined that patients with two to four DM risk factors had a higher risk of NOD compared with those with zero to one risk factor. Conversely, the meta-analysis of 13 trials by Sattar and colleagues, in addition to an analysis of the WHI, determined that elevated BMI did not predispose statin users to NOD.

Women may be more at risk for NOD with statin use. The sex-specific analysis of the JUPITER trial revealed a higher incidence of physician-reported DM in postmenopausal women treated with rosuvastatin (HR 1.49, 95% CI 1.11–2.01; \( P = 0.008 \)) compared with men (HR 1.14, 95% CI 0.91–1.43; \( P = 0.24 \)). The groups, however, were not well matched because the women were older, had a higher BMI, and had a higher incidence of hypertension and metabolic syndrome, compared with the men. Nonetheless, these findings are supported by the aforementioned WHI because statin use among the postmenopausal population was associated with a 48% greater likelihood of NOD.

The meta-analysis by Sattar et al also revealed a higher risk of DM in older statin-treated patients. The mean age range for these individuals was 67 to 76 years and included studies using pravastatin and rosuvastatin. The authors noted that in addition to age, other clinical factors (eg, recent MI, presence of heart failure) in these study populations may have predisposed the subjects to higher rates of NOD.

Numerous other risk factors have been linked to statins and NOD, including populations of Asian descent. The genetic differences in statin pharmacokinetics and pharmacodynamics, as well as a genetic susceptibility to insulin resistance among Asian populations likely play a role. Other potential risk factors for statin-associated DM include patients with a family history of DM and those with a longer duration of statin use.

Possible Mechanisms To Explain Association Of Statins And NOD

Several mechanisms have been proposed explaining the association of statins and NOD: calcium channel blockade in β cells, decreased glucose transporter 4 (GLUT4) expression, diminished levels of coenzyme Q10, and cholesterol uptake in pancreatic β cells. Those discussed most commonly include blocking calcium channels in pancreatic β cells, inhibiting the synthesis of products downstream of HMG-CoA reductase, and reducing the translocation of GLUT4.

When intracellular calcium within pancreatic β cells increases, insulin secretion is initiated. This process is largely controlled by voltage-gated calcium channels. Rat models have demonstrated that simvastatin blocks calcium channels, thereby inhibiting calcium signaling of the pancreatic β cells. Pravastatin also blocked calcium channels in animal models, but only at doses much higher than what is used clinically.

The HMG-CoA reductase inhibition by statins blocks the production of other substances in the cholesterol pathway, including isoprenoids such as dolichol, geranylgeranyl pyrophosphate, farnesyl pyrophosphate, and coenzyme Q10. These substances upregulate GLUT4, which controls insulin-mediated cellular glucose uptake in adipocytes and striated muscle cells. Data indicate that after treatment with clinical doses of atorvastatin, GLUT4 expression was decreased, causing diminished glucose uptake and insulin resistance in adipose, muscle, and liver tissues.

Another proposed mechanism involves the observation that patients with familial hypercholesterolemia (ie, elevated LDL-C) have low rates of DM. In addition, intracellular cholesterol is believed to inhibit cellular function and survival. Statins upregulate LDL receptors to facilitate cholesterol transport. This activity occurs not only in the liver but other tissues, including the pancreas. As such, pancreatic LDL receptor upregulation causes increased intracellular cholesterol levels and potentially toxic effects in β cells.

Residual patient-related factors also warrant consideration for the association between statins and NOD. First, patients may be less motivated to exercise and follow a heart-healthy diet if they believe the medication is addressing their elevated cholesterol. Second, statin users who exercise may experience more intense musculoskeletal symptoms, possibly limiting exercise activity. Both instances could impair glucose homeostasis and result in weight gain, further increasing the likelihood of NOD.

Differences Among Agents

Current evidence supports an association between statins and NOD, but no prospective studies have definitively differentiated individual agents in terms of risk. The available literature is limited and should be interpreted cautiously because of the
retrospective design of most studies. In the aforementioned meta-analyses, Sattar et al found no difference between lipophilic (atorvastatin, simvastatin, and lovastatin) and hydrophilic statins (rosuvastatin and pravastatin), whereas others have found an increased risk with more intensive statin therapy.19,20

The analysis performed by Zaharan and colleagues found an increased risk of NOD with atorvastatin (adjusted HR 1.25, 95% CI 1.21–1.28; \( P < 0.0001 \)), simvastatin (adjusted HR 1.14, 95% CI 1.06–1.23; \( P = 0.0005 \)), and rosuvastatin (adjusted HR 1.42, 95% CI 1.33–1.52; \( P < 0.0001 \)), but not for fluvastatin (adjusted HR 1.04, 95% CI 0.91–1.18; \( P = \text{not significant} \)) or pravastatin (adjusted HR 1.02, 95% CI 0.98–1.06; \( P = \text{not significant} \)).21 Similarly, a retrospective cohort study of a Canadian healthcare database was performed to specifically examine the risk with individual statins.35 This analysis identified 471,250 patients with no history of DM, who were newly prescribed a statin during the 14-year study period. Compared with pravastatin, patients treated with atorvastatin had a 22% increased risk of NOD (adjusted HR 1.22, 95% CI 1.15–1.29), with rosuvastatin having an 18% increased risk (adjusted HR 1.18, 95% CI 1.10–1.26), and with simvastatin had a 10% increased risk (adjusted HR 1.10, 95% CI 1.04–1.17). In contrast, lovastatin (adjusted HR 0.99, 95% CI 0.86–1.14) and fluvastatin (adjusted HR 0.95, 95% CI 0.81–1.11) were not associated with an increased risk. After adjusting for dose, the risk of rosuvastatin was no longer significant (adjusted HR 1.01, 95% CI 0.94–1.09), but the study found the overall risk of NOD to be potency dependent. Although the authors could not account for all risk factors such as weight, family history, or ethnicity, they found risk was similar regardless of whether the statin was used for primary or secondary prevention.

Pitavastatin appears to have promising outcomes in relation to the incidence of NOD.36 A smaller retrospective analysis compared the glycemic control among patients with DM taking atorvastatin 10 mg/day, pitavastatin 2 mg/day, or pravastatin 10 mg/day. Of the three agents, only atorvastatin was found to significantly increase blood glucose and HbA1c levels.37 The Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Intolerance is the first large-scale clinical trial to prospectively examine the effect of a statin on the incidence of DM.38 The multicenter, open-label trial randomized individuals with impaired glucose tolerance to either pitavastatin 1 to 2 mg/day with lifestyle modifications or lifestyle modifications only. Preliminary results show that of 1269 patients, those randomized to the pitavastatin group were less likely to progress from impaired glucose tolerance to DM (HR 0.82, 95% CI 0.68–0.99).

It appears that higher intensity statin therapies such as rosuvastatin, simvastatin, and atorvastatin may have an increased risk of NOD compared with less intensive statins. Because cholesterol guidelines advocate for higher intensity statins, this potential finding is of concern.39 Despite pravastatin, fluvastatin, lovastatin, and pitavastatin appearing to be more favorable in terms of NOD incidence, there is limited high-quality evidence to draw definitive conclusions among agents. This highlights the need for direct comparisons of individual statins and NOD risk, especially at equal intensities.

**Clinical Guide**

Several questions remain regarding statins and NOD, which should be the focus of future studies. In the meantime, we provide several considerations to assist with clinical decision making in hopes of minimizing the potential risk of statin-associated glycemic impairment.

- Screen patients to determine baseline glycemic values. This is especially important among those with risk factors for DM (eg, BMI > 30 kg/m², hypertension, elevated triglycerides, fasting glucose 100–125 mg/dL, family history of DM, ethnic group [eg, Asians]).

- Understand that certain less-intensive statins appear to have minimal impact on glycemic indices. Practitioners may consider these for lower-risk patients, those with risk factors for DM, or individuals concerned with NOD. Studies have generally demonstrated that pravastatin, pitavastatin, fluvastatin, and lovastatin have neutral to modest effects on glycemic markers; however, practitioners should be mindful of lovastatin because of its potential drug interactions. The moderate to maximum daily doses of these “moderate-intensity” statins (pravastatin 40–80 mg, fluvastatin 80 mg, pitavastatin 2–4 mg, lovastatin 40 mg) achieve the 30% to 50% LDL-C reduction suggested by cholesterol guidelines.39,40

- Consider a nonstatin to achieve additional LDL-C reduction. Although they provide greater efficacy, higher statin doses generally demonstrate higher rates of NOD. As a result, practitioners may want to choose a less-intensive statin in certain patients, but are then faced with the dilemma of a diminished ability to reduce LDL-C. The addition of a nonstatin option to the less-intensive statin may help resolve this issue. Also, the need for a nonstatin is frequently encountered when patients are limited in statin dose because of its adverse effects. The addition of ezetimibe or a bile acid resin will further lower LDL-C by approximately 20% and not impair glucose parameters. Ezetimibe is glucose neutral and has demonstrated modest but significant reductions in CV events when added to a statin.41 Bile acid resins effectively reduce HbA1c by approximately 0.5%, but they are limited by poor palatability and the need for separation from other medications.42 Niacin should be avoided if glucose impairment is a concern because studies indicate the agent is associated with a 27% to 37% greater incidence of NOD.43 Proprotein convertase subtilisin kexin type 9 inhibitors are an approved medication class with a likely role in select high-risk populations, such as those with heterozygous familial hypercholesterolemia, to achieve additional LDL-C reduction. Although their future use in the general dyslipidemia population is undetermined at this time, data to this point have not shown an increased risk for NOD.44,45

- Choose concomitant antihypertensive agents wisely. Hypertension is a common comorbidity associated with dyslipidemia. Older agents, specifically β-blockers and thiazide diuretics, increase NOD by 22% to 43%. Conversely, angiotensin-converting enzyme
inhibitors and angiotensin receptor blockers have demonstrated insulin-sensitizing properties and a reduced incidence of NOD, whereas calcium channel blockers are considered glucose neutral. If β-blockade is indicated, agents with additional α-1 vasodilatory properties (eg, carvedilol) minimally affect glycemic markers.43

• Emphasize therapeutic lifestyle changes. Reinforcing the benefits of a healthy diet and regular physical activity cannot be overemphasized. In fact, lifestyle interventions provide marked reductions in NOD,43 are approximately twice as effective as metformin at preventing NOD,46 and have been shown to persist for up to several years.43 In addition to improving glycemic markers, lifestyle modifications improve blood pressure and beneficially affect all major lipoproteins.47

Conclusions

Meta-analyses of RCTs generally indicate a small to moderate risk of NOD with statin therapy, whereas observational studies report a more substantial association. Several mechanisms have been proposed, but additional studies are needed to fully elucidate possible causes. The incidence of NOD appears to be related to both the dose and potency of the statin and is greater among patients with underlying risk factors for DM. Well-designed studies are needed to better comprehend this association and determine potential differences among individual statins. The general consensus is that the benefits of statin therapy outweigh the risk of glycemic impairment, especially among patients with high CV risk. Several clinical considerations can be implemented to minimize the risk of statin-associated NOD, including screening individuals before initiating statin therapy and using certain agents that appear to affect glycemic indices less negatively.

References


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