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Role of Statins in Glucose Homeostasis and Insulin Resistance

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Abstract Statins are widely used for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD), and, under the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guidelines, more individuals are eligible for statin therapy. In this review, we summarize evidence for a mild increase in serum glucose and increased incidence of diabetes associated with statins, the hypothesized mechanisms by which statins may impair glucose homeostasis, the risk of diabetes associated with particular statins, and the net effect on ASCVD risk. As emphasized by the ACC/AHA guideline group and other experts, the risk-reducing benefits of statin therapy generally outweigh the mild rise in glucose levels or new diagnoses of diabetes. As such, an appropriate balancing of benefits and risks is critical in clinical practice as clinicians engage patients in shared decision making. Moreover, when discussing statins and risk of diabetes, this is a prime opportunity for clinicians to provide further counseling on the central importance of weight loss and adhering to a healthy lifestyle in glucose homeostasis and diabetes prevention.

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Introduction

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guidelines recommend the use of pooled cohort equations to determine the risk of atherosclerotic cardiovascular (CV) disease (ASCVD), and subsequent prescription of statins for primary and secondary prevention after a clinician-patient risk discussion [1••, 2•]. Approximately 56 million individuals may be eligible for statin therapy under the new 2013 ACC/AHA guidelines [3], and statins are the most widely prescribed medication in the USA [4]. The largest contributor to ASCVD risk using the pooled cohort equations is age, leading to higher numbers of statin-eligible patients in older age groups. Even in the younger age group of 40–59 years without CV disease, 30 % would be eligible for statin therapy for primary prevention [3]. However, more than 77 % of individuals in the older age group of 60–75 years would be eligible for statin therapy [3]. Since stroke is now an endpoint of the ASCVD risk score and African Americans are more likely than Caucasians to sustain a future cerebrovascular event, many more African Americans will qualify for a clinician-patient risk discussion than before, even with seemingly good or normal lipid levels.

Statins are generally well tolerated, yet they are not void of side effects. There are some concerns about alterations in glucose homeostasis, with a slightly higher incidence of new diagnoses of diabetes mellitus (DM) seen in large epidemiologic studies and placebo controlled trials of patients on statin therapy, especially with evidence of insulin resistance or glucose intolerance at baseline. Also, the Food and Drug Administration (FDA) in February 2012 warned patients and healthcare professionals regarding the

potential increased risk of impaired glycemic control or a new diagnosis of type 2 diabetes with the use of statins [5]. Diabetes is a significant risk factor for ASCVD, and it is imperative that the net reduction in risk to the patient be understood since the reduction in major adverse cardiovascular events (MACE) is significantly greater than the increase in new cases of diabetes.

In individuals who have diabetes risk factors (such as BMI ≥30 kg/m^2, fasting glucose ≥100 mg/dL, and metabolic syndrome), statins increase the likelihood of developing diabetes and can accelerate the diagnosis of diabetes by approximately 5 weeks due to a small hyperglycemic effect [2•, 6•]. In individuals with pre-existing ASCVD, these risk factors also seem to play a role in predicting a new diagnosis of diabetes [7].

There have been multiple studies and meta-analyses examining the link between statin therapy and glucose homeostasis. In this review, we summarize evidence for a mild increase in serum glucose and increased incidence of diabetes associated with statins, the hypothesized mechanisms by which statins may impair glucose homeostasis, the risk of diabetes associated with particular statins, and the net effect on ASCVD risk.

Association Between Statin Therapy and Impaired Glucose Homeostasis

In 2008, the JUPITER (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial showed that patients randomized to rosuvastatin 20 mg per day had a slightly higher hemoglobin A1c at trial completion (5.9 versus 5.8 %, $p = 0.001$) compared to patients randomized to placebo [8]. There was also a mild increase in new diagnoses of diabetes (3.0 versus 2.4 %, $p = 0.01$) [8]. In a post hoc analysis, Ridker et al. showed that individuals with major risk factors for the development of diabetes had an increase in the incidence of new diagnoses of diabetes with the use of a high-intensity statin compared to those individuals without a major risk factor [6•]. However, the investigators concluded that the benefits of statin therapy outweigh the mild rise in hemoglobin A1c or new diagnoses of diabetes [6•], which is similar to the recommendations by the FDA (Tables 1 and 2).

Other data have suggested that the rise in serum glucose and new diagnoses of diabetes are more common in patients taking high-intensity statins and therefore may be proportional to the relative lowering of low-density lipoprotein cholesterol (LDL-C). Carter et al. conducted a population-based retrospective cohort study to examine the association between various statins and new-onset diabetes [9]. Compared to patients treated with pravastatin, patients treated with the more potent atorvastatin experienced a 22 % increase in the relative risk of new-onset diabetes [9]. Similarly, there was an increased risk of new-onset diabetes with rosuvastatin and simvastatin; however, treatment with fluvastatin or lovastatin did not demonstrate an increased risk [9].

Table 1 Comparison of net cases of new DM and adverse cardiovascular events in 12 statin trials for primary or secondary prevention of ASCVD

Ref #	Study name	Year	Statin, dose	Number of patients	Follow-up (years)	Absolute increase in new DM (statin vs. placebo)	Absolute decrease in MACE (statin vs. placebo)	Study endpoint
[43]	4S	1994	Simvastatin 10–40 mg	4242	5.2	5 (198 vs. 193)	191 (431 vs. 622)	Major coronary event
[13, 44]	WOSCOPS	1995	Pravastatin 40 mg	5974	4.8	−18 (75 vs 93)	74 (174 vs. 248)	Coronary death or non-fatal MI
[45]	AFCAPS/ TexCAPS	1998	Lovastatin 20–40 mg	6211	5.2	−2 (72 vs. 74)	67 (116 vs. 183)	Sudden cardiac death, MI, or unstable angina
[46]	LIPID	1998	Pravastatin 40 mg	6997	5.9	-12 (126 vs 138)	158 (557 vs 715)	Coronary death or non-fatal MI
[47]	GISSI-Prevenzione	2000	Pravastatin 20 mg	3460	1.9	−9 (96 vs. 105)	16 (120 vs. 136)	Death, non-fatal stroke, or MI
[48]	HPS	2002	Simvastatin 40 mg	14,573	5	42 (335 vs. 293)	552 (2033 vs. 2585)	Major coronary event, stroke, or revascularization
[49]	PROSPER	2002	Pravastatin 40 mg	5023	3.2	38 (165 vs. 127)	65 (473 vs. 408)	Coronary death, non-fatal MI, or stroke
[50]	ALLHAT-LLT	2002	Pravastatin 40 mg	6087	4.8	26 (238 vs. 212)	41 (380 vs. 421)	Coronary death or non-fatal MI
[51]	ASCOT-LLA	2003	Atorvastatin 10 mg	7773	3.3	20 (154 vs. 134)	54 (100 vs. 154)	Coronary death or non-fatal MI
[52]	MEGA	2006	Pravastatin 10–20 mg	6086	5.3	8 (172 vs. 164)	35 (66 vs. 101)	Cardiac or sudden death, MI, or revascularization
[8]	JUPITER	2008	Rosuvastatin 20 mg	17,802	1.9	54 (270 vs. 216)	109 (142 vs. 251)	Cardiac death, non-fatal MI, stroke, hospitalization for unstable angina, or revascularization

Diabetes diagnostic criteria included adverse events or physician report, treatment with glucose-lowering therapy, and fasting blood glucose ≥126 mg/dL

DM diabetes mellitus, *ASCVD* atherosclerotic cardiovascular disease, *MACE* major adverse cardiovascular events, *MI* myocardial infarction

Table 2 Summary of hypothesized mechanisms of statin-associated glucose homeostasis and insulin resistance

Reference number	Study	Year	Proposed mechanism
[15]	Goldfine	2012	Statins cause impaired insulin secretion from pancreatic beta cells, decreased activity of insulin-signaling proteins in adipocytes, and reduced expression of glucose transporters.
[17]	Nowis et al	2014	Statins produce cholesterol-dependent conformational changes in GLUT, mainly GLUT type 4, thereby increasing serum glucose levels.
[18, 20]	Brault et al; Yada et al	2014; 1999	Chronic use of lipophilic statins may decrease cholesterol in pancreatic beta cells, thereby blocking L-type calcium channels and inhibiting glucose-induced calcium signaling. This may inhibit insulin secretion and reduce synthesis of ubiquinone, which leads to decreased ATP production and delayed insulin release, resulting in elevated postprandial glucose levels.
[32]	Swerdlow et al	2015	Carriers of HMG-CoA reductase gene single nucleotide polymorphisms tend to have lower LDL-C levels, increased BMI, and an increased prevalence of type 2 DM compared to subjects who were carriers of alleles. The development of type 2 DM with statins could likely be due to inhibition of HMG-CoA reductase.
[33]	Besseling et al	2015	Statins cause increased LDL-R expression, promoting transmembrane cholesterol transport; thereby, causing pancreatic beta cell function to be impaired due to increased cellular uptake of cholesterol.

GLUT glucose transporter, *ATP* adenosine triphosphate, *HMG-CoA* 3-hydroxy-3-methyl-glutaryl-coenzyme A, *LDL-C* low-density lipoprotein cholesterol, *BMI* body mass index, *DM* diabetes mellitus, *LDL-R* low-density lipoprotein receptor

In a pooled analysis of nine trials involving participants who already carried a diagnosis of type 2 diabetes, Erqou et al. showed that hemoglobin A1c was mildly higher in participants on statin therapy (either atorvastatin, pravastatin, or simvastatin) compared to placebo [10]. The pooled hemoglobin A1c was 7.53 % in the statin groups compared to 7.41 % in the control group [10]. Additionally, a retrospective cohort study in Taiwan by Lin et al. involving patients with acute coronary syndrome (ACS) who had undergone percutaneous coronary intervention suggested a 27 % proportional increase in incident diabetes with statin therapy [11].

In contrast, the recent Heart Outcomes Prevention Evaluation (HOPE)-3 trial did not show any significant impact of statin therapy on new-onset diabetes [12]. In this trial, 6361 individuals were assigned to rosuvastatin 10 mg daily and 6344 individuals were assigned to the placebo group [12]. New-onset diabetes occurred in 232 individuals (3.9 %) in the rosuvastatin group versus 226 individuals (3.8 %) in the placebo group ($p = 0.82$) [12].

Other randomized controlled trial results were acceptable with respect to statins and glucose homeostasis. In the West of Scotland Coronary Prevention Study (WOSCOPS) [12, 13] of pravastatin 40 mg versus placebo, the pravastatin group had a reduced risk of diabetes diagnosis [13]. Moreover, a subanalysis of the LIVALO Effectiveness and Safety (LIVES) study involving 308 participants with type 2 diabetes demonstrated an absolute decrease in hemoglobin A1c levels of 0.28 % ($p < 0.001$) [14].

Hypothesized Mechanisms by Which Statins Impair Glucose Homeostasis

Knowledge gaps exist regarding the mechanisms of impaired glucose homeostasis associated with statin therapy and LDL-C reduction, though several hypotheses have been suggested. Goldfine recently proposed multiple mechanisms including impaired insulin secretion from pancreatic beta cells, decreased activity of insulin-signaling proteins in adipocytes, and reduced expression of glucose transporters (GLUT) [15, 16]. Furthermore, Nowis et al. suggested that the cholesterol activity of statins may also be related to their effects on glucose homeostasis by producing cholesterol-dependent conformational changes in GLUT [17], mainly GLUT type 4, thereby increasing serum glucose levels [18].

Another major hypothesis is that statins increase the risk of diabetes by increasing insulin resistance and altering homeostasis between insulin secretion and insulin sensitivity [19].

Chronic use of lipophilic statins (such as atorvastatin, lovastatin, or simvastatin) may decrease cholesterol in pancreatic beta cells, thereby blocking L-type calcium channels and inhibiting glucose-induced calcium signaling. This may inhibit insulin secretion [20] and reduce synthesis of ubiquinone [18]. Decreased levels of ubiquinone, which is a vital constituent of insulin signaling, may lead to decreased beta cell adenosine triphosphate (ATP) production and delayed insulin release, resulting in elevated postprandial glucose levels [18].

Adiponectin and leptin have received some attention in their role as mediators in the diabetogenic effect of statins; however, no clear conclusion has been made, and there is more ongoing research in this area currently [21–24]. A recent meta-analysis of 43 randomized controlled trial arms suggested that a reduction in adiponectin expression is unlikely to be an explanation for statin-associated new-onset diabetes [25]. Another adipokine, leptin, is vital in the regulation of body weight and is mostly produced in adipose tissue [26]. Leptin inhibits insulin secretion via multiple ways: suppression of preproinsulin messenger ribonucleic acid (mRNA), inhibition of glucagon-like peptide-1 (GLP-1)-induced insulin production, impairment of GLUT 2, regulation of ATP-sensitive potassium channels, and impairment of GLUT 4 translocation, which promotes insulin resistance [27–30]. The clinical importance of leptin with respect to statins and glucose homeostasis remains uncertain.

The rise in serum glucose due to statins may be directly related to their mechanism of action, yet independent from their cholesterol-lowering effects. Kain et al. proposed that by blocking 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, simvastatin leads to accumulation of acetyl CoA, a precursor of fatty acid synthesis [31]. The subsequent intracellular buildup of fatty acids appears to affect the insulin-signaling pathway, leading to increased insulin resistance [31].

Clues to the mechanisms of statin-mediated impaired glucose homeostasis may also lie in genetic studies of families with polymorphisms in the HMG-CoA reductase gene [32]. Swerdlow et al. reported that carriers of HMG-CoA reductase gene single nucleotide polymorphisms (SNP) tended to have lower LDL-C levels, larger waist circumferences, heavier body weights, and a higher prevalence of type 2 diabetes compared to subjects who were carriers of wild type alleles [32].

Another proposed mechanism by Besseling et al. is LDL receptor-mediated transmembrane cholesterol transport [33]. In a cross-sectional study in the Netherlands, the investigators found that the prevalence of diabetes was lower in individuals with familial hypercholesterolemia versus their unaffected relatives (1.75 versus 2.93 %, $p < 0.001$) [33], with variability by mutation type. It appeared that individuals with mutations leading to more severe familial hypercholesterolemia phenotypes, and thus reduced transmembrane cholesterol transport, were least likely to have diabetes. Importantly, statin inhibition of HMG-CoA reductase increases LDL receptor (LDL-R) expression, thereby promoting transmembrane cholesterol transport [33].

Risk of Diabetes Associated with Particular Statins

There has also been significant discussion regarding the effect a specific dose and type of statin medication on the absolute risk of newly diagnosed diabetes. Erqou et al. showed that across multiple studies, there was moderate heterogeneity observed between the risk of diabetes associated with particular statin medications, with atorvastatin (10 or 20 mg) having a stronger effect on new-onset diabetes compared to pravastatin or simvastatin ($p = 0.014$) [10]. Preiss et al. showed a relative increase of 12 % in incident diabetes in participants treated with simvastatin 80 mg or atorvastatin 80 mg compared with lower-intensity doses of atorvastatin in five randomized clinical trials [34]. However, there was also a decrease in the number of ASCVD events with the higher-intensity statins compared to the lower-intensity statins [34].

Carter et al. also showed that patients who were treated with higher-intensity statins (such as atorvastatin, rosuvastatin, and simvastatin) had an increased incidence of new-onset diabetes compared to patients treated with fluvastatin or lovastatin over a 14-year study period [9]. A large meta-analysis by Navarese et al. showed that pravastatin had the lowest rate of incident diabetes while rosuvastatin had the highest rate, which correlates with their expected degrees of non-high-density lipoprotein cholesterol (HDL-C) reduction [35]. Higher doses of individual statins were also associated with an increased incidence of new diabetes, suggesting a dose-dependent effect [35].

Net Effect on Risk of ASCVD Due to Statin Therapy Plus a Mild Increase in Serum Glucose

The benefits versus true adverse effects of statin therapy have been recently thoroughly reviewed by Rory Collins and colleagues in *Lancet* [36]. Based on data from large randomized trials, it was estimated that a reduction in LDL-C by 2 mmol/L (77 mg/dL) would lead to a 10 % absolute benefit in secondary prevention in patients with established ASCVD and a 5 % absolute benefit in patients being treated for primary prevention of ASCVD over the course of 5 years of therapy [36]. Treatment with a high-intensity statin (i.e., atorvastatin 40 mg) is expected to also cause an absolute increase in incidence of diabetes of 0.5–1.0 % [36]. Treatment of 1000 patients with atorvastatin 40 mg daily would lead to prevention of 50–100 strokes, heart attacks, or deaths due to coronary artery disease, and 5–10 cases of new diabetes, most likely in patients with

pre-existing risk factors for diabetes [36]. The absolute risk of ASCVD events is also higher in diabetic patients, and they may have even more benefit from statin therapy than patients without diabetes [37]. There have also been no increases in the risk of microvascular disease in kidneys [38, 39] or eyes (EXCEL and 4S, EMPATHY) [40–42] with statin therapy or the associated mild increase in serum glucose.

Conclusion

For the most part, statins are well-tolerated medications, and their relationship with new-onset diabetes or rise in hemoglobin A1c appears to be fairly small, and mostly negligible in individuals without predisposition. In individuals with metabolic syndrome, statin use may increase the hemoglobin A1c mildly, leading to accelerated progression to the threshold used for the diagnosis of diabetes. The underlying incidence of new-onset diabetes in the primary prevention trials has been about 0.5–1 % per year, and the mean increase in hemoglobin A1c in patients on rosuvastatin 20 mg daily in the JUPITER trial was 0.1 % [36]. However, further evaluation of long-term effects of statin-induced diabetes is warranted, including the effect of statin therapy on microvascular complications of diabetes, which thus far have not been increased with statin use. Meanwhile, it is also important to maintain emphasis on lifestyle modifications, such as physical activity and healthy dietary habits, to prevent the development of diabetes.

The current ACC/AHA guidelines do not recommend discontinuing statins in diabetic patients, as the associated rise in average serum glucose is generally mild or modest. Specifically, the panel stressed that the "occurrence of a major ASCVD event represents a much greater harm to health status than does an increase in blood glucose leading to a diagnosis of diabetes" [1••]. In their safety label change in 2012, the FDA also pointed out that the CV benefits of statins usually outweigh the nominal risk of diabetes [5].

As such, an appropriate balancing of benefits and risks is critical in clinical practice as clinicians engage patients in shared decision making, present evidence, exercise clinical judgment, and consider patient preferences to reach thoughtful therapeutic decisions. Finally, when discussing statins and diabetes, this is a prime opportunity for clinicians to provide further counseling on the central importance of weight loss and adhering to a healthy lifestyle, such as avoiding sugar-laden beverages, eating plenty of vegetables, and partaking in physical activity, in glucose homeostasis and diabetes prevention.

Compliance with Ethical Standards

Conflict of Interest Drs Dahagam, Hahn, Goud, D'Souza, Abdelqader, and Blumenthal have no conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain studies with human or animal subjects performed by the author.

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