**Reviewer’s Comments**

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### DIABETOGENIC EFFECT OF STATINS: MOLECULAR MECHANISMS

**ABSTRACT**

Statins, hydroxymethyl glutaryl coenzyme A reductase (HMG CoA) inhibitors,are potent hypolipidemic drugs. They are widely used in the primary and secondary prevention of cardiovascular diseasesand some of the most commonly prescribed medications worldwide. Statin therapy is associated with a modest increase in the risk of new-onset diabetes after long term therapy, and there has been great interest in the possible mechanisms for this adverse effect. Multiple molecular mechanisms have been proposed primarily related to increased insulin resistance and decreased insulin secretion. The risk for statin-related diabetes depends on many factors including age, pre-existing diabetic risk, type and potency of statin. But the consensus is that the benefits of statins in preventing cardiovascular disease events clearly outweigh the potential risk of diabetes.The aim of this review is to give underlying pathomechanisms and clinical relevance of diabetogenic effect of statins.

*Key words*: statins, diabetogenicity,adverse effect, mechanism, risk

**INTRODUCTION**

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, and hypercholesterolemia is one of the major CVD risk factors1. Statins (HMGCoA) reductase inhibitors) were first approved by the US Food and Drug Administration (FDA) in 1987 and remain the first-choice drugs for their potent cholesterol-lowering effects.Since then statins have become the most prescribed drugs worldwide2,3. In addition to lowering LDL-C, statins have shown pleiotropic effects facilitating cardioprotective properties including improvement of endothelial dysfunction, antioxidant properties, inhibition of inflammation and stabilization of atherosclerotic plaques4-8.Other pleiotropic mechanisms of statins are improvement of bone diseases and central nervous system diseases7. On the other hand, despite well - known clinical benefit of statins on CV prevention, their possible adverse effects cannot be disregarded9-11.As the prescription rates for statins have increased, more adverse effects have been identified, with the most common being increased liver enzymes and myopathy1. However, major statin trials indicate a definite increase in the development of new-onset diabetesmellitus (NODM) with statin therapy, especially in the presence of pre-existing diabetic risk factors, such as older age, obesity, woman, impaired glycemic control and insulin resistance, patients with lower baseline LDL(low density lipoprotein)-C levels, lower achieved LDL-C levels, and a large LDL-C level reduction10,12.Data suggest a 10-22%higher risk of NODMwith statin use compared to nonusers. The risk increases with intensive treatment13,14.While this effect has been thought to be a drug class effect, recent data suggest that pravastatin and pitavastatin could exhibit neutral effects on glycaemic parameters in patients with and without diabetes13.

Type 2 diabetes mellitus (T2DM) is a strong, independent risk factor for CV outcomes15. As T2DM is accompanied by dyslipidemia, statins have a major role in preventing the long term complications in diabetes and are recommended for diabetics with normal LDL-C levels as well16.The benefits of statins on CV risk reduction outweigh any harm related to their diabetogenic effect.

Currently, there are seven statin drugs available on the market: Pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin, fluvastatin and lovastatin. They are classified according to their hydrophobicity into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (atorvastatin, fluvastatin, lovastatin, pitavastatin and simvastatin).

NODM risk was first demonstrated in the JUPITER trial (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluation Rosuvastatin)  in 2008,and then greater attention has been given to this issue17,18. Since that time the literature has largely supported this increased risk with other statins as well19-23.Treatment with high doses resulted in a further increase by 10%, but there were no new cases of NODM among patients with no diabetes risk factors at baseline in JUPITER study24.In March 2012, the FDA decided there was sufficient evidence to warrant a warning about increased diabetes risk being added to the packaging of all statins25. It appears though that the risk of diabetes is limited to people already at high risk for developing diabetes such as the elderly, women, obese, those with the metabolic syndrome, Asian ancestry, and patients with CVD and hypertension26-28. The trials did not indicate an increased risk of diabetes-related complications, such as nephropathy, neuropathy and retinopathy with statin therapy.

The effects of different statins on the risk of NODM are controversial. In the first two years of regular statin use, Dormuthh et al.29 reported that higher potency statin use is associated with a moderate increase in the risk of NODMcompared with lower potency statins in patients treated for secondary prevention of CVD. It appears the risk is in parallel with their HMGCoA reductase inhibition capacity. It was suggested that lipophilic statins are more diabetogenic than the hydrophilic ones29-31.Although structural differences based on lipophilic or hydrophilic features have been proposed to be the possible mechanisms of stain-induced NODM9 recentclinical studies have demonstrated no apparent difference in the diabetogenic effects between lipophilic and hydrophilic statins32.Thuswe need more datato determine potential differences among individual statins. Accumulating evidence from several statin trials, population-based studies, clinical studies, and *in vitro* studies suggests that pravastatin is the least diabetogenic statin33.In a new cohort study, compared with rosuvastatin, less diabetogenic effect of pitavastatin were observed among patients treated with moderate-intensity statin regimen32.

**Molecular mechanisms**

Studies suggest that the effect of statins on glucose homeostasis reflect inhibition of HMGCoA reductase. *In vitro* and *in vivo*data indicate that statins reduce synthesis of mevalonate pathway products leading to impaired pancreatic β-cell function and decreased insulin sensitivity and insulin release, but the exact mechanism(s) of diabetogenesis are still unclear13.It seems decreased insulin secretion is the majorcontributor to statin-induced diabetes1,34,35. Several molecular mechanisms have been proposed: Certain statins affect insulin secretion through direct, indirect or combined effects on calcium channels in pancreatic β-cells; Downregulation of GLUT4 results in hyperglycemia; Decreases important downstream products, such as coenzyme Q10, farnesyl pyrophosphate, geranylgeranyl pyrophosphate and their depletion leads to reduced intracellular signalling. Other possible mechanisms areinhibition of adipocyte differentiation, modulation of leptin and adiponectin. Genetic links and epigenetic regulations via differential expression of specific microRNAshave alsoimportant roles1,14,32,36.

**Pancreatic β-Cells andL-type Ca2+ channels**

It is well known that opening of voltage gated Ca2+ (CaV; L-type ) channels have an important role in insulin secretion in the pancreatic β-cells. Functional changes or levels of Ca2+channels impair glucose homeostasis7. It is suggestedthat chronic inhibition of cholesterol biosynthesis may disrupt the functional activity of CaV channels and insulin secretory granule mobilization and membrane fusion37.There is no clear mechanism proposed for this phenomena however these effects may be due to conformational changes of the channel subunits1,14,23.

On the other hand, statins exert their beneficial pleiotropic effects on the CV system by activating ATP-dependent potassium (KATP)channels in the CVtissue. However, simultaneous activation of KATP channels in the pancreatic β-cells leads to inhibition of insulin release which may lead to diabetes38.

**Glucose transportersand caveolin**

Statins can reduce mRNA and protein expression of GLUT2 (glucose transporter 2: predominant isoform in β-cells)and CaV channel, thereby inhibiting insulin synthesis and secretion. Intracellular glucose uptake via GLUT2 initiates phosphorylation by glucose kinase and subsequently KATP and CaV channel - mediated signalling cascades for the synthesis and secretion of insulin. Inhibition of HMG CoA reductase by statin can suppress synthesis of isoprenoids which in turn also inhibits the expression of GLUT4 (another rate-limiting protein for glucose transport), leading to impaired glucose uptake.In the late adipocyte differentiation stages, it was demonstrated a decrease in caveolin-1, an important plasma membrane protein present in caveolae-rich regions where GLUT4 is translocated upon stimulation by insulin 1,12. Khan et al39reported an inhibition of caveolar vesicle docking in mice treated with simvastatin. Takaguri et al40 also found that after atorvastatin, but not pravastatin treatment, total GLUT4 level and the translocation were altered. Decreased glucose uptake and increased insulin resistance in adipose tissue, muscle and liver which may be due to reduced translocation of GLUT4, and consequently leads to hyperglycemia14.

**Insulin Receptor Substrate and Insulin Signalling**

Several disturbances in insulin signal transduction mediated by statin treatment have been described in different tissues leading to insulin resistance14. It is suggested that statins reduces insulin signal transduction via inhibition of necessary phosphorylation events and altering cellular distribution of small G proteins1. Insulin receptor substrate (IRS-1) is critical for insulin signalling and is phosphorylated in response to insulin binding to the insulin receptor (IR). Through the phosphatidylinositol 3-kinase (PI3K) pathway, Akt becomes phosphorylated and mediates glucose uptake by controlling GLUT4 translocation to the plasma membrane. Atorvastatin treatment decreased phosphorylation of IRS-1 and Akt in a dose-dependent manner. Lovastatin has been shown to inhibit the phosphorylation of the IR β-subunit and prevent the association of PI3K with the IRS-1/IR complex. Another study found that atorvastatintreatment downregulated IRS-1 and IR β-subunit levels during adipocyte differentiation. However, Takaguri et al40found no change in mRNA level, protein expression or phosphorylation of IR in adipocytes treated with atorvastatin or pravastatin. They observed changes in GLUT4 with atorvastatin, and concluded that inhibition of its translocation was not due to changes in IR, but rather the intracellular transduction of the signal. The proteins RhoA and Rab4 are small G proteins involved in the insulin signal transduction via modification of IRS-1 and Akt phosphorylation. Rab4 is crucial for glucose transport. In adipocytes, it is involved in the transport of GLUT4 to the plasma membrane in response to insulin signals. Takaguri etal40 have reported that decreased GLUT4 membrane expression by atorvastatin is partially mediated by loss of Rab4 function.

**Ubiquinone, adiponectin and leptin**

Recent evidence also highlights the role of ubiquinone (CoQ10), adiponectin and leptin, in the modulation of glucose metabolism. Statins may impair glucose metabolism via affecting on CoQ10, adiponectin and leptin12.CoQ10 plays an important role in the regulation of mitochondrial function, which is critical for β-cell function. Statin therapy has been shown to reduce the production of CoQ10, and potentially induce myopathy, but it is unclear whether this contributes to impaired insulin sensitivity and increase risk of diabetes. CoQ10 has been shown to ameliorate the reduction in GLUT4 transporter by simvastatin in adipocytes41. More research is needed to determine whether supplementation of CoQ10 can prevent the development of diabetes especially in patients with preexisting diabetic risk and receiving statin therapy. According to the some experimental data CoQ10 administration improves pancreatic β-cell function, increases insulin sensitivity and preserves the mitochondrial function in the cells42.

A decrease in adiponectin level might also link statin therapy to insulin resistance and diabetes.However, the role of adiponectin has not been clearly established10,12. Adiponectin is secreted by adipocytes, and low adiponectin levels are associated with insulin resistance and obesity.Evidence suggests that adiponectin may protect against the development of diabetes by improving insulin sensitivity12,35. Proposed molecular mechanisms of the effect of adiponectin on insulin sensitivity include inhibition of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, stimulation of glucose uptake and fatty acid oxidation in the skeletal muscle10. However, clinical studies have been inconclusive, with increases, decreases, and no change in adiponectin levels by statin therapy35. It is unclear whether lipophilic and hydrophilic statins have differential effect on adiponectin metabolism. In contrast to lipophilic statins, hydrophilic statins (pravastatin, rosuvastatin and pitavastatin) are generally more consistent to increase adiponectin levels and insulin resistance.Pitavastatin has consistently been shown to increase adiponectin levels and, in some studies, it improves insulin sensitivity12,35.

Leptin, an important satiety factor in appetite regulation is also secreted by adipocytes and has been shown to be suppressed by atorvastatin, rosuvastatin, and simvastatin, but not by pravastatin or pitavastatin, in humans35,43. Statin use is associated with increased calorie intake and weight gain. Decreases in leptin expression by statins may contribute, at least in part, to increases in food intake in the long term statin users. But the role of statins in regulation of leptin is still conflicting43.

**Inflammation**

Inflammation can promote insulin resistance and /or diabetes44. Statins are generally anti-inflammatory, but HMGCoA reductase inhibition and targeted decrease in protein prenylation predominantly result in skewing immune responses toward anti-inflammatory characteristics, via pleiotropic effect. Statin use reduces in C-reactive protein which has been associated with a reduction of myocardial infarction risk12.In addition to CRP, statins have been shown to reduce many inflammatory processes, including cell adhesion/migration and skewing cytokine profiles. They reduce pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6.But, the findings have shown that statins increase the pro-inflammatory cytokine, IL-1β, via decreased protein prenylation in immune cells. IL-1β can be regulated by the NLRP3 inflammasome containing caspase-134. It is hypothesized (“inflammatory hypothesis of statins”) that, under dysmetabolic conditions, statins might have pro-inflammatory effects via induction of certain inflammasomes. On certain conditions, statins may activate inflammasome NLRP3 from macrophages or adipocytes in the presence of endotoxins, leading to IL-mediated insulin resistance.However, under physiological states, a moderate decrease in insulin sensitivity can be compensated by enhanced insulin secretion by pancreatic β-cells. This concept requires more study34.

**Geneticlink**

Genetic studies suggest that the increased risk of NODM may be partially explained by gene variants in the target genes for LDL-C lowering drugs.There is evidence that HMG CoA reductase single nucleotide polymorphisms (SNPs) is associated with a small but discernible increase in the risk of diabetes, raised ﻿blood﻿ glucose and insulin, and higher body weight33,35,45,.This observation was validated in the randomized statin trials, and one particular allele was associated with a significant increase in the risk of new diabetes. A recent randomization study (Mendelian study)reported that the inhibition of HMG CoA reductase activity with statin, particularly due to genetic variation in the HMGCR gene (rs17238484 and rs12916 alleles), was associated with an increased risk of NODM12,33,and this may at least partly explain their diabetogenic effect33-35.

On the other hand, statins are associated with epigenetic changes, including histone acetylation,

miRNA regulation, and DNA methylation (DNAm), particularly at genes related to lipid and insulin metabolism46.Arecent epigenome - wide association study has investigated the association between statinuse and changes in DNAm at sites inthe genome called CpGs and found an evidence on DNAm partially mediating statins’ effects. This could be one potential mechanism linking statin therapy and NODM46.

Increased hepatic gluconeogenesis has been suggested as one of the primary mechanism for statin- induced glucose intolerance. However, the precise mechanism is not well known yet. Since aging is the primary risk factor in NODM, aging related molecules may be involved in glucose dysregulation caused by statin. Agingrelated molecule Sirt6 has been reported to repress hepatic gluconeogenesis.In a recent study simvastatininduced miR-495 (a novel inhibitor of Sirt6) and down regulatedSirt6 expression, which leads to enhancement of FoxO1-mediated hepatic gluconeogenesis in mice liver. mRNA levels of gluconeogenesis genes such as Pck1, G6pc, and Ppargc1a were increased in the statin-treated liver. Thus, Shi et al.47 have suggested that Sirt6 activation may offer a promising strategy for preventing NODM.

**DISCUSSION and CONCLUSION**

Since the publication of the JUPITER trial, attention has been focused on the adverse glycemic effects of statin therapy.Whilemolecular basis remains unclearit appears that the potential diabetogenic effects of statins may involve multiple mechanisms.*In vitro* and population studies have revealed possible explanations. Potentiating insulin resistance (increased hepatic gluconeogenesis, inhibition of GLUT4 translocation and of adipocyte differentiation) or decreased insulin secretion (the direct or indirect effects on β - cell function)have been proposed as major mechanisms9,12,45. There is also evidence of an association between alleles influencing lipid metabolism and the risk of diabetes.Intense research is currently going on to elucidate the mechanisms of statin- induced NODM at the molecular level48.

Intensive statin therapy is more diabetogenic than moderate-intensity therapy. The possible determining factors are the drug characteristics (potency, dose), patient characteristics (kidney function, age, cardiovascular risk) and the pre-diabetic state.Although statin therapy is associated with a modest increase in the risk (about one per thousand patient-years), the consensus is that the benefits of statins in preventing CVD events clearly outweigh the potential risk of diabetes.Before initiation of statin therapy the risk of NODM should be assessed in patients10,13. During therapy, high risk of patients should be monitored for changes in blood glucose. In addition, diet and lifestyle interventions should be emphasized to reduce the risk of NODM.Diabetes is diagnosed only 2-4 months earlier in statin-treated patients, and if diabetesdevelops, it should be managed according to the guidelines13,16,35.On the other hand, diabetic patients are one of the groups that benefits most from statin therapy with regards to CV risk, and statins are recommended in patients with diabetes and hypercholesterolemia, to prevent CV events49.Indiabetes of long duration, the effect of statins on glycaemic control is small and unlikely to be clinically important.Thus, diabetic individuals should receive statin treatment to reduce CVD.Considering the important effect in diminishing CV risk in all patients, including those with diabetes, it is not recommended to stop the statin therapy in patients with pre-existing or newly diagnosed diabetes. Patients who develop NODM while using statins do not exhibit increased microvascular disease15,50.On the other hand,since elderly people have a shorter life expectancy and more comorbidities than younger people, statins may have fewer benefits in this population. Thus, the benefits and disadvantages ofstatins should be evaluated carefully in elderly individuals49.

**REFERENCES**

1. Brault M, Ray J, Gomez YH, [Mantzoros](https://pubmed.ncbi.nlm.nih.gov/?term=Mantzoros+CS&cauthor_id=24641882) CS, [Daskalopoulou](https://pubmed.ncbi.nlm.nih.gov/?term=Daskalopoulou+SS&cauthor_id=24641882)SS. Statin treatment and new-onset diabetes: a review of proposed mechanisms. Metabolism 2014; 63: 735–745.[*https://doi.org/10.1016/j.metabol.2014.02.014*](https://doi.org/10.1016/j.metabol.2014.02.014)
2. Anyanwagu U, Idris I, Donnelly R. Drug-Induced Diabetes Mellitus: Evidence for Statins and Other Drugs Affecting Glucose Metabolism [Clin Pharmacol Ther](https://www.ncbi.nlm.nih.gov/pubmed/?term=Anyanwagu+U%2C++Idris+I++Donnelly+R+2015) 2016; 99(4): 390-400.[*https://doi.org/10.1002/cpt.274*](https://doi.org/10.1002/cpt.274)
3. Ramkumar S, Raghunath A, Raghunath S. [Statin therapy: Review of safety and potential side effects.](https://www.ncbi.nlm.nih.gov/pubmed/27899849)Acta Cardiol Sin 2016; 32(6): 631-639.[*https://doi.org/10.6515/acs20160611a*](https://doi.org/10.6515/acs20160611a)
4. Cumaoğlu A, Ozansoy G, Irat AM, Arıcıoğlu A, Karasu C, Arı N.[Effect of long term, non cholesterol lowering dose of fluvastatin treatment on oxidative stress in brain and peripheral tissues of streptozotocin-diabetic rats.](https://www.ncbi.nlm.nih.gov/pubmed/21172345)Eur J Pharmacol 2011; 654(1): 80-5.[*https://doi.org/10.1016/j.ejphar.2010.11.035*](https://doi.org/10.1016/j.ejphar.2010.11.035)
5. [Davignon J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Davignon%20J%5BAuthor%5D&cauthor=true&cauthor_uid=15198965). Beneficial cardiovascular pleiotropic effects of statins. [Circulation](https://www.ncbi.nlm.nih.gov/pubmed/15198965) 2004; 109(23 Suppl 1): III39-43
6. Kavalipati N, Shah J, Ramakrishan A, Vasnawala H. [Pleiotropic effects of statins.](https://www.ncbi.nlm.nih.gov/pubmed/26425463)Indian J Endocrinol Metab 2015; 19(5): 554-62. [*https://doi.org/10.4103/2230-8210.163106*](https://doi.org/10.4103/2230-8210.163106)
7. [Muscogiuri G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Muscogiuri%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25208056), [Sarno G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sarno%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25208056), [Gastaldelli A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gastaldelli%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25208056), *et al*. The good and bad effects of statins on insulin sensitivity and secretion. [Endocr Res](https://www.ncbi.nlm.nih.gov/pubmed/25208056)  2014; 39(4): 137-43.[*https://doi.org/10.3109/07435800.2014.952018*](https://doi.org/10.3109/07435800.2014.952018)
8. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins[on the cardiovascular system.](https://www.ncbi.nlm.nih.gov/pubmed/28057795)Circ Res 2017; 120(1): 229-243.[*https://doi.org/10.1161/CIRCRESAHA.116.308537*](https://doi.org/10.1161/CIRCRESAHA.116.308537)
9. Núñez-Cortés JM, Amenós AC, Gimilio JFA, *et al*. [Consensus on the statin of choice in patients with impaired glucose metabolism: Results of the DIANA Study.](https://www.ncbi.nlm.nih.gov/pubmed/27837448) Am J Cardiovasc Drugs 2017; 17(2): 135-142.[*https://doi.org/10.1007/s40256-016-0197-9*](https://doi.org/10.1007/s40256-016-0197-9)
10. Cybulska B, Kłosiewicz-Latoszek L. [How do we know that statins are diabetogenic, and why? Is it an important issue in the clinical practice?](https://www.ncbi.nlm.nih.gov/pubmed/30067279)Kardiol Pol. 2018; 76(8): 1217-1223.[*https://doi.org/10.5603/KP.a2018.0150*](https://doi.org/10.5603/KP.a2018.0150)
11. Pinal-Fernandez I, Casal-Dominguez M, Mammena AL. Statins: pros and cons. Med Clin (Barc) 2018; 150(10): 398–402.[*https://doi.org/10.1016/j.medcli.2017.11.030*](https://doi.org/10.1016/j.medcli.2017.11.030)
12. Chan DC, Pang J, Watts GF. [Pathogenesis and management of the diabetogenic effect of statins: a role for adiponectin and coenzyme Q10?](https://www.ncbi.nlm.nih.gov/pubmed/25398645)Curr Atheroscler Rep 2015; 17(1): 472.[*https://doi.org/10.1007/s11883-014-0472-7*](https://doi.org/10.1007/s11883-014-0472-7)
13. Carmena R, Betteridge DJ.[Diabetogenic action of statins: Mechanisms.](https://pubmed.ncbi.nlm.nih.gov/31037345/) Curr Atheroscler Rep 2019; 21(6): 23.[*https://doi.org/10.1007/s11883-019-0780-z*](https://doi.org/10.1007/s11883-019-0780-z)
14. [Galicia-Garcia](https://pubmed.ncbi.nlm.nih.gov/?term=Galicia-Garcia+U&cauthor_id=32630698) U, [Jebari](https://pubmed.ncbi.nlm.nih.gov/?term=Jebari+S&cauthor_id=32630698) S, [Larrea-Sebal](https://pubmed.ncbi.nlm.nih.gov/?term=Larrea-Sebal+A&cauthor_id=32630698) A*,  et al*. Statin treatment-induced development of Type 2 diabetes: From clinical evidence to mechanistic insights. Int J Mol Sci 2020;21(13):4725. *https://doi.org/*[*10.3390/ijms21134725*](https://doi.org/10.3390/ijms21134725)
15. Ray K.Statin diabetogenicity: guidance for clinicians.Cardiovasc Diabetol 2013; 12(Suppl 1): S3.
16. [Chogtu B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chogtu%20B%5BAuthor%5D&cauthor=true&cauthor_uid=25789118), [Magazine R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Magazine%20R%5BAuthor%5D&cauthor=true&cauthor_uid=25789118), [Bairy KL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bairy%20KL%5BAuthor%5D&cauthor=true&cauthor_uid=25789118). Statin use and risk of diabetes mellitus. [World J Diabetes](https://www.ncbi.nlm.nih.gov/pubmed/25789118) 2015; 6(2): 352-7. [*https://doi.org/10.4239/wjd.v6.i2.352*](https://doi.org/10.4239/wjd.v6.i2.352)
17. [Ridker](https://www.ahajournals.org/doi/full/10.1161/CIRCOUTCOMES.109.868299) PM**.** The JUPITER Trial**.** Results, controversies, and implications for prevention. Circulation: Cardiovascular Quality and Outcomes. 2009; (2):279–285.[*https://doi.org/10.1161/CIRCOUTCOMES.109.868299*](https://doi.org/10.1161/CIRCOUTCOMES.109.868299)
18. Ridker PM, Danielson E, Fonseca FA, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359(21):2195-207.[*https://doi.org/10.1056/NEJMoa0807646*](https://doi.org/10.1056/NEJMoa0807646)
19. Benes LB, Bassi NS, Davidson MH.The risk of hepatotoxicity, new onset diabetes andrhabdomyolysis in the era of high-intensity statintherapy: Does statin type matter? Progress in Cardiovasc Dis 2016; 59:145-152.[*https://doi.org/10.1016/j.pcad.2016.08.001*](https://doi.org/10.1016/j.pcad.2016.08.001)
20. Culver AL, [Ockene IS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ockene%20IS%5BAuthor%5D&cauthor=true&cauthor_uid=22231607), [Balasubramanian R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Balasubramanian%20R%5BAuthor%5D&cauthor=true&cauthor_uid=22231607), *et al*.  Statin use and risk of diabetes mellitus in postmenopausal women in the Women’s Health Initiative. Arch Intern Med 2012; 172: 144-152[*https://doi.org/10.1001/archinternmed.2011.625*](https://doi.org/10.1001/archinternmed.2011.625)
21. Sattar N, Taskinen MR. [Statins are diabetogenic--myth or reality?](https://www.ncbi.nlm.nih.gov/pubmed/22818818)Atheroscler Suppl 2012; 13(1):1-10.[*https://doi.org/10.1016/j.atherosclerosissup.2012.06.001*](https://doi.org/10.1016/j.atherosclerosissup.2012.06.001)
22. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative metaanalysis of randomised statin trials. Lancet 2010; 375:735-42.[*https://doi.org/10.1016/S0140-6736(09)61965-*6](https://doi.org/10.1016/S0140-6736(09)61965-6)
23. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol 2016; 24: 67(20):2395-2410.[*https://doi.org/10.1016/j.jacc.2016.02.071*](https://doi.org/10.1016/j.jacc.2016.02.071)
24. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012; 380:565-71.[*https://doi.org/10.1016/S0140-6736(12)61190-8*](https://doi.org/10.1016/S0140-6736(12)61190-8)
25. U.S. Food and Drug Administration. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. FDA Drug Safety Communication. <http://www.fda.gov/Drugs/ DrugSafety/ucm293101.htm>
26. Bell DSH, Di Nicolantonio JJ, O’Keefe JH. Is statin-induced diabetes clinically relevant? A comprehensive review of the literature. Diabetes, Obesity and Metabolism 2014; 16:689–694. [*https://doi.org/10.1111/dom.12254*](https://doi.org/10.1111/dom.12254)
27. Chrysant SG. New onset diabetes mellitus induced by statins: Current evidence. Postgraduate Medicine 2017; 129(4): 430-435.[*https://doi.org/10.1080/00325481.2017.1292107*](https://doi.org/10.1080/00325481.2017.1292107)
28. [Wallemacq C. Statins and new-onset diabetes : Benefit-risk balance.](https://pubmed.ncbi.nlm.nih.gov/31436061/) Rev Med Suisse 2019; 15 (659): 1454-1457.
29. [Dormuth CR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dormuth%20CR%5BAuthor%5D&cauthor=true&cauthor_uid=24874977), [Filion KB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Filion%20KB%5BAuthor%5D&cauthor=true&cauthor_uid=24874977), [Paterson JM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Paterson%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=24874977),*et al*. Higher potency statins and the risk of new diabetes: Multicentre, observational study of administrative databases. BMJ 2014; 348:g3244. [*https://doi.org/10.1136/bmj.g3244*](https://doi.org/10.1136/bmj.g3244)
30. Agouridis AP, Kostapanos MS, Elisaf MS. [Statins and their increased risk of inducing diabetes.](https://www.ncbi.nlm.nih.gov/pubmed/26437128)Expert Opin Drug Saf 2015; 14(12): 1835-44.[*https://doi.org/10.1517/14740338.2015.1096 343*](https://doi.org/10.1517/14740338.2015.1096%20343)
31. Guertin JR, Rahme E, LeLorier J. [Use of continuous exposure variables when examining dose-dependent pharmacological effects - Application to the association between exposure to higher statin doses and the incidence of diabetes.](https://www.ncbi.nlm.nih.gov/pubmed/28186711)J Popul Ther Clin Pharmacol 2017; 24(1):5-15. [*https://doi.org/10.22374/1710-6222.24.1.1*](https://doi.org/10.22374/1710-6222.24.1.1)
32. Liu WT, Lin C, Tsai MC et al. Effects of pitavastatin, atorvastatin and rosuvastatin on the risk of new-onset diabetes mellitus: A single-center cohort study. Biomedicines 2020; 8:499.[*https://doi.org/10.3390/biomedicines8110499*](https://doi.org/10.3390/biomedicines8110499)
33. [Laakso M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Laakso%20M%5BAuthor%5D&cauthor=true&cauthor_uid=28155189), [Kuusisto J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kuusisto%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28155189). Diabetes secondary to treatment with statins. C[urr Diab Rep](https://www.ncbi.nlm.nih.gov/pubmed/28155189) 2017; 17(2):10. [*https://doi.org/10.1007/s11892-017-0837-8*](https://doi.org/10.1007/s11892-017-0837-8)
34. Ganda OP. Statin-induced diabetes: incidence, mechanisms, and implications. F1000Research 2016; 5(F1000 Faculty Rev):1499. [*https://doi.org/10.12688/f1000research.8629.1*](https://doi.org/10.12688/f1000research.8629.1)
35. [Robinson JG](https://www.ncbi.nlm.nih.gov/pubmed/?term=Robinson%20JG%5BAuthor%5D&cauthor=true&cauthor_uid=25887679). Statins and diabetes risk: how real is it and what are the mechanisms? [Curr Opin Lipidol.](https://www.ncbi.nlm.nih.gov/pubmed/25887679)  2015; 26(3):228-35.[*https://doi.org/10.1097/MOL.0000000000000172*](https://doi.org/10.1097/MOL.0000000000000172)
36. Paseban M, [Butler](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Butler%2C+Alexandra+E)AE,  [Sahebkar](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Sahebkar%2C+Amirhossein) A.Mechanisms of statin-induced new-onset diabetes. J Cell Physiol 2019; 234: 12551-12561.[*https://doi*](https://doi)*.org/*[*10.1002/jcp.28123*](https://doi.org/10.1002/jcp.28123)
37. Xia F, Xie L, Mihic A, *et al*. Inhibition of cholesterol biosynthesis impairs insulin secretion and voltage-gated calcium channel function in pancreatic beta-cells. Endocrinology 2008; 149: 5136–45.[*https://doi.org/10.1210/en.2008-0161*](https://doi.org/10.1210/en.2008-0161)
38. [Sehra D](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sehra%20D%5BAuthor%5D&cauthor=true&cauthor_uid=28571494), [Sehra S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sehra%20S%5BAuthor%5D&cauthor=true&cauthor_uid=28571494), [Sehra ST](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sehra%20ST%5BAuthor%5D&cauthor=true&cauthor_uid=28571494). Cardiovascular pleiotropic effects of statins and new onset diabetes: is there a common link: do we need to evaluate the role of KATP channels? [Expert Opin Drug Saf.](https://www.ncbi.nlm.nih.gov/pubmed/28571494)  2017; 7:823-831. [*https://doi.org/*10.1080/14740338.2017.1338269](https://doi.org/10.1080/14740338.2017.1338269)
39. Khan T, Hamilton MP, Mundy ID, Chua SC, Scherer PE. Impact of simvastatin on adipose tissue: Pleiotropiceffects *in vivo*.Endocrinology2009;150: 5262–5272.  [*https://doi*](https://doi)*.org/*[*10.1210/en.2009-0603*](https://dx.doi.org/10.1210%2Fen.2009-0603)
40. [Takaguri](https://pubmed.ncbi.nlm.nih.gov/?term=Takaguri+A&cauthor_id=18469500) A, [Satoh](https://pubmed.ncbi.nlm.nih.gov/?term=Satoh+K&cauthor_id=18469500) K, [Itagaki](https://pubmed.ncbi.nlm.nih.gov/?term=Itagaki+M&cauthor_id=18469500) M, [Tokumitsu](https://pubmed.ncbi.nlm.nih.gov/?term=Tokumitsu+Y&cauthor_id=18469500) Y, [Ichihara](https://pubmed.ncbi.nlm.nih.gov/?term=Ichihara+K&cauthor_id=18469500) K. Effects of atorvastatin and pravastatin on signal transduction related to glucose uptake in 3T3L1 adipocytes. J Pharmacol Sci 2008; 107(1):80-89. [*https://doi.org/10.1254/jphs.fp0072403*](https://doi.org/10.1254/jphs.fp0072403)
41. Ganesan S, Ito MK. Coenzyme Q10 ameliorates the reduction in GLUT4 transporter expression induced by simvastatin in 3T3-L1 adipocytes. Metab Syndr Relat Disord 2013; 11:251-5.[*https://doi.org/10.1089/met.2012.0177*](https://doi.org/10.1089/met.2012.0177)
42. Schroeder MM, Belloto Jr RJ, Hudson RA, McInerney MF. Effects of antioxidants coenzyme Q10 and lipoic acid on interleukin-1β-mediated inhibition of glucose-stimulated insulin release from cultured mouse pancreatic islets. Immunopharmacol Immunotoxicol 2005; 27:109-22.[*https://doi.org/10.1081/iph-51755*](https://doi.org/10.1081/iph-51755)
43. Singh P, Zhang Y, Sharma P, *et al*. [Statins decrease leptin expression in human white adipocytes.](https://pubmed.ncbi.nlm.nih.gov/29372612/)Physiol Rep 2018; 6(2):e13566.[*https://doi.org/10.14814/phy2.13566*](https://doi.org/10.14814/phy2.13566)*.*
44. [Henriksbo BD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Henriksbo%20BD%5BAuthor%5D&cauthor=true&cauthor_uid=26451278), [Schertzer JD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Schertzer%20JD%5BAuthor%5D&cauthor=true&cauthor_uid=26451278).Is immunity a mechanism contributing to statin-induced diabetes? [Adipocyte](https://www.ncbi.nlm.nih.gov/pubmed/26451278)  2015; 4(4):232-8.[*https://doi.org/10.1080/21623945.2015.1024394*](https://doi.org/10.1080/21623945.2015.1024394)
45. [Collins](https://www.ncbi.nlm.nih.gov/pubmed/?term=Collins%20PD%5BAuthor%5D&cauthor=true&cauthor_uid=27864787) PD,[Sattar](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sattar%20N%5BAuthor%5D&cauthor=true&cauthor_uid=27864787) N.Glycaemic effects of non-statin lipid-lowering therapies.[Curr Cardiol Rep](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5116040/) 2016; 18(12): 133.*https://doi.org/*[*10.1007/s11886-016-0795-9*](https://dx.doi.org/10.1007%2Fs11886-016-0795-9)
46. Ochoa-Rosales C, Portilla-Fernandez E, Nano J *et al*, Epigenetic link between statin therapy and type 2 diabetes. Diabetes Care 2020; 43:875-884.[*https://doi.org/10.2337/dc19-1828*](https://doi.org/10.2337/dc19-1828)
47. [Shi](https://pubmed.ncbi.nlm.nih.gov/?term=Shi+MY&cauthor_id=33052223) MY, [Bang](https://pubmed.ncbi.nlm.nih.gov/?term=Bang+IH&cauthor_id=33052223) IH, [Han](https://pubmed.ncbi.nlm.nih.gov/?term=Han+CY&cauthor_id=33052223) CY, [Lee](https://pubmed.ncbi.nlm.nih.gov/?term=Lee+DH&cauthor_id=33052223) DH, [Park](https://pubmed.ncbi.nlm.nih.gov/?term=Park+BH&cauthor_id=33052223) BH, [Bae](https://pubmed.ncbi.nlm.nih.gov/?term=Bae+EJ&cauthor_id=33052223) EJ. Statin suppresses sirtuin 6 through miR-495, increasing FoxO1-dependent hepatic gluconeogenesis. Theranostics 2020; 10(25):11416-11427.*https://doi.org/*[*10.7150/thno.49770*](https://doi.org/10.7150/thno.49770)
48. [Yandrapalli S, Malik A, Guber K, *et al*. Statins and the potential for higher diabetes mellitus risk.](https://pubmed.ncbi.nlm.nih.gov/31474169/) Expert Rev Clin Pharmacol 2019; 12(9):825-830.[*https://doi.org/10.1080/17512433.2019.1659133*](https://doi.org/10.1080/17512433.2019.1659133)
49. Horodinschi RN, Stanescu AMA, Bratu OG,*et al*. Treatment with statins in elderly patients. Medicina (Kaunas, Lithuania) 2019; 55(11):72.*https://doi.org/*[*10.3390/medicina55110721*](http://dx.doi.org/10.3390/medicina55110721)
50. [Betteridge](https://pubmed.ncbi.nlm.nih.gov/?term=Betteridge+DJ&cauthor_id=26668119) DJ, [Carmena](https://pubmed.ncbi.nlm.nih.gov/?term=Carmena+R&cauthor_id=26668119) R.The diabetogenic action of statins - mechanisms and clinical implications. Nat Rev Endocrinol 2016;12(2):99-110.[*https://doi.org/10.1038/nrendo.2015.194*](https://doi.org/10.1038/nrendo.2015.194)