

## REVIEW

# How do we know that statins are diabetogenic, and why? Is it an important issue in the clinical practice?

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## Abstract

There is no doubt nowadays that statins exert a diabetogenic action. The evidence comes from observational studies, randomised trials, and meta-analyses. The relationship between statin use and new-onset type 2 diabetes is associated with statin potency and dose. It seems also to be stronger if the lowering effect is stronger and the low-density lipoprotein cholesterol level achieved is lower. The mechanisms underlying the development of diabetes in statin-treated patients are not completely understood. Generally, the increased insulin resistance and decreased insulin secretion are taken into account. However, it should be kept in mind that the cardiovascular risk reduction effect of statins outweighs the harm related to diabetes induction. The patients at risk of diabetes development should be monitored with regard to the parameters of glucose metabolism. The introduction of preventive lifestyle modifications to prevent diabetes is recommended. New-onset diabetes should be managed according to the guidelines.

**Key words:** statins, diabetogenic effect, observational studies, randomised trials, mechanisms, recommendations

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## INTRODUCTION

Observational studies [1–6], controlled clinical trials [7, 8], and meta-analyses [9–14] indicate that statins induce diabetes, and intensive statin therapy is more diabetogenic than moderate-intensity therapy [15, 16]. This issue has been of interest only since 2008, when a primary prevention trial with rosuvastatin was published, showing a 44% reduction in the rate of cardiovascular events versus placebo (relative risk [RR] 0.56; 95% confidence interval [CI] 0.46–0.69) but also a 25% higher risk of diabetes (RR 1.25; 95% CI 1.05–1.49) [7]. At the time of that publication, statins had already been in use for 20 years. These findings prompted a search for associations between statin treatment and the risk of diabetes in other studies, as well as for possible underlying pathomechanisms.

## OBSERVATIONAL STUDIES

Observational studies showed an increase in the risk of type 2 diabetes in statin users compared to non-users, which was higher than in randomised clinical trials.

In the Women's Health Initiative study, an association between incident diabetes and statin use was evaluated in

153,840 postmenopausal women aged 50 to 79 years without diabetes at baseline [2]. Statins were taken by 10,884 of these women (7.04% of the study population). Statin use at baseline was associated with a 48% higher risk of incident type 2 diabetes (hazard ratio [HR] 1.48, 95% CI 1.38–1.59) during more than one million person-years of follow-up (adjusted for many potential confounders). All statins were diabetogenic. Diabetes was self-reported.

The METSIM study cohort included 8749 subjects aged 45 to 73 years without diabetes at baseline [3]. The median duration of follow-up was 5.9 years. The risk of diabetes among statin users was 46% higher compared to non-users (HR 1.46, 95% CI 1.22–1.74). Insulin sensitivity was lower by 24%, and  $\beta$ -cell function (disposition index) was lower by 12%. Most statin users were treated with simvastatin (65.9%), followed by atorvastatin (18.1%), rosuvastatin (8.6%), fluvastatin (3.8%), lovastatin (2.3%), and pravastatin (1.3%).

Diabetes was diagnosed based on fasting blood glucose levels, oral glucose tolerance test, HbA1c levels, or initiation of hypoglycaemic therapy during follow-up. Of note, this study was designed to evaluate the effect of statins on the risk of type 2 diabetes and not the risk of cardiovascular disease.

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In a retrospective study on a Korean population, based on the Korean National Health Insurance registry, cases of new-onset diabetes mellitus were evaluated in patients with ischaemic heart disease in whom statin therapy was initiated [4]. Statins were taken by 94,370 patients who were compared to 61,990 statin non-users. The follow-up period was from January 2010 to December 2012. During this time, incident type 2 diabetes was nearly twice as common among statin users (HR 1.84, 95% CI 1.63–2.09, adjusted for treatment intensity, individual drugs, and comorbidities). Regarding individual statins, atorvastatin, rosuvastatin, simvastatin, and lovastatin use was associated with twofold higher risk of diabetes. The lowest risk was seen for pravastatin (HR 1.54, 95% CI 1.32–1.81). Data on incident diabetes were based on cases identified during the follow-up and prescription of one or more hypoglycaemic drugs.

Results of the observational Australian Longitudinal Study on Women's Health, regarding cases of incident diabetes in elderly women treated with statins, have been recently published [5]. The analysis included 8372 Australian women aged 76 to 82 years without diabetes at baseline. Of these, 49% were treated with statins, most commonly with atorvastatin followed by simvastatin. The mean duration of statin therapy was 6.5 years. The risk of new-onset diabetes among statin users was 33% higher compared to non-users (HR 1.33, 95% CI 1.04–1.70). A dose-response effect was noted, with HR of 1.17 (95% CI 0.84–1.65) in women treated with low statin doses compared to HR of 1.51 (95% CI 1.14–1.99) in those treated with high doses.

Lately, Italian authors published a meta-analysis of observational studies that evaluated the association between statin use and the risk of new-onset diabetes [6]. Publications from inception to 30 June 2016 were assessed, and the inclusion criteria for the meta-analysis were met by 18 observational studies and two case-control studies. The median duration of follow-up was 7.2 years. The risk of incident diabetes was 44% higher in statin users compared to non-users (RR 1.44, 95% CI 1.31–1.58). A high heterogeneity among studies was noted. Regarding individual statins, the highest risk of incident diabetes was associated with the use of rosuvastatin and atorvastatin (RR 1.61, 95% CI 1.30–1.98; and RR 1.49, 95% CI 1.31–1.70, respectively). Simvastatin use was associated with a 38% higher risk of diabetes (RR 1.38, 95% CI 1.19–1.61). Pravastatin and fluvastatin were associated with the same diabetogenic effect (RR 1.39, 95% CI 1.09–1.77). Thus, the meta-analysis has confirmed that the diabetogenic effect of statin is a class effect.

### CLINICAL TRIALS AND THEIR META-ANALYSES

As mentioned above, the first study to indicate a diabetogenic effect of statins was the JUPITER study [7]. It was a randomised clinical trial that evaluated primary prevention of cardiovascular disease using rosuvastatin 20 mg daily versus placebo.

The median duration of follow-up was 1.9 years. The trial was interrupted prematurely due to a highly significant 44% reduction in the rate of cardiovascular events (RR 0.56, 95% CI 0.46–0.69,  $p < 0.00001$ ). However, a post hoc analysis revealed an excess of patients with newly diagnosed type 2 diabetes in the rosuvastatin group, at the rate of 3% (270 cases per 8901 patients in the rosuvastatin group) versus 2.4% in the placebo group (216 cases per 8901 patients).

The authors also analysed the rates of incident diabetes in relation to the presence of risk factors for diabetes. Four risk factors were taken into account: metabolic syndrome, increased fasting glucose (100–125 mg/dL), body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, and HbA1c level  $> 6\%$ . In patients without risk factors for type 2 diabetes ( $n = 6095$ ), the risk was not increased compared to placebo (HR 0.99, 95% CI 0.45–2.21). In contrast, the risk of incident diabetes was 28% higher in those with one or more risk factors for diabetes ( $n = 11,508$ ; HR 1.28, 95% CI 1.07–1.54).

Of note, however, a significant reduction in the rate of cardiovascular events was noted in both groups (with or without risk factors for diabetes): by 39% (HR 0.61, 95% CI 0.47–0.79,  $p = 0.0001$ ) and 52% (HR 0.48, 95% CI 0.33–0.68,  $p = 0.001$ ), respectively.

In patients with risk factors for diabetes, 134 cardiovascular events and deaths were avoided at the cost of 54 cases of new diabetes, while 86 cardiovascular events were avoided without any cases of new diabetes in patients with no risk factors for diabetes. Incident diabetes was physician-reported.

Recently, the results of a randomised clinical trial, the Diabetes Prevention Program (DPP) study, have been reported regarding risk of developing diabetes in patients who were or were not treated with a statin during the trial (a post hoc analysis) [8]. The DPP trial tested the effect of intensive lifestyle intervention, metformin, or placebo on the incidence of diabetes in patients at high risk of diabetes ( $n = 3234$ ). At baseline, statin was used in only 4% of the participants compared to 33% patients in the lifestyle intervention group, 37% patients in the metformin group, and 35% patients in the placebo group at 10 years of follow-up. Simvastatin and atorvastatin were the most commonly used statins (in 40% and 37% of statin-treated patients, respectively). Statin use was associated with a 36% higher risk of diabetes (HR 1.36; 95% CI 1.17–1.58), and an increase in the risk of diabetes during statin treatment was noted in all three intervention groups. Diabetes was diagnosed based on annual oral glucose tolerance tests and semi-annual fasting blood glucose measurements.

A comprehensive review paper regarding the association of statin therapy with incident diabetes has been published lately [9]. To summarise, it could be said that in the majority of the large randomised primary and secondary prevention trials involving different statins with data available (respectively eight and five), no significant increase in the relative risk of new-onset diabetes was observed. There was a significant

association of statin treatment with incident diabetes in two trials (JUPITER, PROSPER). Only one primary prevention study revealed a significant decrease in the risk of diabetes (WOSCOPS).

Since 2009, a number of meta-analyses have provided data on the diabetogenic effect of statins, indicating an ongoing interest in this issue. While the trials included were primarily designed to evaluate the effects of statins on the risk of cardiovascular events, post hoc analyses compared occurrence of incident diabetes in statin users and non-users as well as in patients receiving intensive versus moderate-intensity statin treatment. Below, we summarise the results of these meta-analyses in chronological order based on the publication date.

In 2009, Rajpathak et al. [10] reported a meta-analysis of six clinical trials that included 57,593 patients. The mean duration of follow-up was 3.9 years. Statin use was associated with a 13% higher risk of diabetes compared to control (RR 1.13, 95% CI 1.03–1.23), without heterogeneity among trials. The next meta-analysis (2010) included 13 trials with 91,140 patients [11]. The mean duration of follow-up was four years. The risk of diabetes among statin users was modestly increased (by 9%; odds ratio [OR] 1.09, 95% CI 1.02–1.17). Statin treatment in 255 patients for four years was associated with one case of incident diabetes. In 2011, a meta-analysis of 76 randomised statin clinical trials was performed to evaluate the effect of these drugs on the risk of cardiovascular disease [12]. Information on incident diabetes was provided in 17 trials. The increase in the risk of diabetes was the same as in the meta-analysis by Sattar et al. [13] (OR 1.09, 95% CI 1.02–1.17). A year later a meta-analysis of 72 randomised statin trials, done partly by the same authors, was conducted to evaluate adverse effects associated with statin use. Information on incident diabetes was provided in 16 of these trials [13]. During a mean follow-up of 2.7 years, similarly to the previous meta-analysis, the risk of diabetes in statin users was 9% higher compared to controls (OR 1.09, 95% CI 1.02–1.16). This meta-analysis was based on the same trials as the previous one. Regarding the effect of individual statins, except for rosuvastatin no data were available or the differences in risk were not significant. Rosuvastatin use (a meta-analysis of four trials) was associated with a significant 14% increase in the risk of diabetes (OR 1.14, 95% CI 1.01–1.29) [13].

Another meta-analysis published in 2013 evaluated the effect of various statins and their doses on the risk of developing incident diabetes [14]. The meta-analysis included 17 clinical trials with 113,394 patients. The duration of follow-up in these studies was more than one year, and statin therapy was compared to placebo, or intensive statin therapy was compared to moderate-intensity treatment. Among statins tested in the included trials, the lowest risk of diabetes versus placebo was noted for pravastatin 40 mg per day (OR 1.07, 95% CI 0.86–1.30). Rosuvastatin 20 mg per day was associated with a 25% higher risk (OR 1.25, 95% CI 0.82–1.90),

and atorvastatin 80 mg per day was associated with a 15% increase in the risk of diabetes (OR 1.15, 95% CI 0.90–1.50). Despite a trend for a higher risk of diabetes among patients treated with intensive statin therapy, these differences were not statistically significant.

A recently published meta-analysis (2016) included 29 trials with 163,039 patients, including 141,863 participants with no diabetes at baseline (18 trials) [15]. The median duration of follow-up was 4.8 years. A direct meta-analysis showed that statins as a class increased the risk of diabetes by 12% (OR 1.12, 95% CI 1.05–1.21). A network meta-analysis revealed that a significant risk of diabetes was associated with the use of atorvastatin 80 mg per day (OR 1.34, 95% CI 1.14–1.57), followed by rosuvastatin (OR 1.17, 95% CI 1.02–1.35). In contrast, the results for simvastatin 80 mg per day and combined doses of individual statins were not significant. Compared with moderate-intensity treatment, intensive statin therapy was associated with a 12% higher risk of diabetes (seven studies; OR 1.12, 95% CI 1.01–1.24). Lipophilic statins were associated with a higher risk of diabetes compared to placebo (OR 1.14, 95% CI 1.02–1.28). However, no increase in the risk was noted in a head-to-head comparison with hydrophilic statins (OR 1.05, 95% CI 0.9–1.23) [15].

#### INTENSIVE VERSUS MODERATE-INTENSITY STATIN THERAPY

Although some of the above studies also evaluated the effect of intensive statin therapy versus moderate-intensity treatment on the risk of new-onset diabetes, studies focused specifically on this issue are also available. These include meta-analyses by Preiss et al. [16] and Waters et al. [17]. The former was a meta-analysis of five statin trials that included 32,752 patients [16]. The duration of follow-up was longer than one year. Intensive statin therapy included atorvastatin 80 mg per day and simvastatin 80 mg per day, and the moderate-intensity treatment group included patients treated with pravastatin 40 mg per day, atorvastatin 10 mg per day, or simvastatin 20 to 40 mg per day. Compared to moderate-intensity treatment, intensive statin therapy was associated with a higher risk of diabetes (OR 1.12, 95% CI 1.04–1.22) and a lower risk of cardiovascular events (OR 0.84, 95% CI 0.75–0.94). The other meta-analysis included two secondary prevention trials, i.e. TNT and IDEAL [17], which, too, were included in the analysis by Preiss et al. [16]. However, this analysis also took into consideration incident diabetes in relation to the presence of risk factors for diabetes (fasting blood glucose > 100 mg/dL, triglyceride level > 150 mg/dL, BMI > 30 kg/m<sup>2</sup>, and a history of hypertension). It was found that intensive atorvastatin therapy, compared to moderate-intensity treatment, did not lead to an increased risk of diabetes in patients with 0 to 1 risk factors for diabetes (HR 0.97, 95% CI 0.77–1.22). In contrast, the risk of diabetes was increased in patients with 2 to 4 risk factors for diabetes (HR 1.24, 95% CI 1.08–1.42).

Reduction in the rate of cardiovascular events with atorvastatin 80 mg per day, compared to moderate-intensity treatment, was higher in both patient subgroups, i.e. with 0 to 1 or 2 to 4 risk factors for diabetes (HR 0.87, 95% CI 0.755–0.995; and HR 0.82, 95% CI 0.71–0.96, respectively). For one additional case of diabetes, 204 patients with 2 to 4 risk factors for diabetes had to receive intensive atorvastatin therapy for one year, while 242 patients had to be treated this way to avoid one cardiovascular event.

#### **ASSOCIATION BETWEEN THE RISK OF INCIDENT DIABETES DURING STATIN THERAPY AND A REDUCTION IN LDL-CHOLESTEROL LEVEL**

This issue may be indirectly related to compliance with statin therapy, as evaluated in 84,828 residents of the Italian Lombardy region, who were newly prescribed with a statin in 2003 to 2004 and had their treatment compliance evaluated based on the number of days the drug was used (by pill counting at follow-up visits) [18]. The mean duration of follow-up per patient was 5.5 years. Incident diabetes was identified based on initiation of anti-diabetic medication.

Compared to very low compliance with statin therapy, the rate of incident diabetes in patients with low, moderate, and good compliance increased by 24% (95% CI 12%–37%), 72% (95% CI 56%–90%), and 95% (95% CI 60%–139%), respectively. Assuming that incident diabetes was completely unrelated to statin therapy in patients with very low treatment compliance, the proportion of diabetes attributable to statin use was 19% (95% CI 11%–27%), 42% (95% CI 36%–47%), and 49% (95% CI 38%–58%), respectively, in patients with low, moderate, and good compliance with statin therapy.

As can be noted above, the risk of incident diabetes increased progressively with increasing compliance with statin therapy. At the same time, however, the risk of macrovascular complications of diabetes decreased progressively with increasing compliance with this type of treatment.

Recent meta-analyses have also evaluated the association between the reduction in low-density lipoprotein cholesterol (LDL-C) level during statin therapy and the risk of new-onset diabetes [19], and between achieved lipid levels and the risk of diabetes [20].

The first of these meta-analyses included 14 statin trials ( $n = 91,140$ ), including eight studies with target LDL-C level  $< 100$  mg/dL (2.59 mmol/L) or LDL-C level reduction by at least 30%, and showed that the rate of incident diabetes during four years of treatment was related to LDL-C level reduction [19]. No increase in the rate of incident diabetes was noted in patients with LDL-C level reduction by less than 20% or 20% to 30% compared to baseline, while the risk of diabetes was increased in patients with LDL-C level reduction by  $> 30%$  to 40% and  $> 40%$  to 50% (OR 1.13, 95% CI 1.01–1.25; and OR 1.29, 95% CI 1.13–1.47, respectively). In terms of absolute risk, one additional case of diabetes was

identified per 137 patients with LDL-C level reduction by 30% to 40% and per 108 patients with LDL-C level reduction by 40% to 50%.

The association between statin therapy and the risk of incident diabetes was stronger in older patients, women, and patients with lower baseline LDL-C levels, lower achieved LDL-C levels, and a large LDL-C level reduction.

The authors concluded that LDL-C level reduction was the most relevant indicator of the risk of statin-induced diabetes. Higher reduction of baseline LDL-C level was associated with a higher risk of diabetes, particularly with LDL-C level reduction by more than 30%.

Earlier, the same authors performed another meta-analysis of the same 14 trials and showed that the rate of new-onset diabetes during four years of statin therapy was related to the achieved LDL-C levels [20]. The risk of diabetes was 33% higher (OR 1.33, 95% CI 1.14–1.56) in patients with the achieved LDL-C level  $\leq 70$  mg/dL (1.8 mmol/L), and 16% higher (OR 1.16, 95% CI 1.06–1.28) in those with the achieved LDL-C level of 70–100 mg/dL (1.8–2.59 mmol/L). The risk of diabetes was not increased in statin-treated patients with the achieved LDL-C level above 100 mg/dL.

#### **MECHANISMS OF THE DIABETOGENIC EFFECT OF STATINS**

Mechanisms by which statins might lead to the development of diabetes are unclear. Potential mechanisms include impaired insulin secretion and increased insulin resistance [9, 21]. This concept is supported by the results of the abovementioned METSIM study, which showed that a 46% higher risk of diabetes (HR 1.46, 95% CI 1.22–1.74) in statin users compared to non-users was accompanied by a 12% reduction in insulin secretion and a 24.3% increase in insulin resistance [3]. Both these differences compared to statin non-users were significant at  $p = 0.001$ . Of note, these adverse effects were related to the statin dose in patients treated with simvastatin or atorvastatin.

However, it is difficult to offer a truly comprehensive view regarding that matter because our understanding of the mechanisms underlying statin-induced reduction of insulin sensitivity and insulin secretion is still far from complete.

##### ***Reduced insulin secretion***

Betteridge and Carmena discussed mechanisms of the diabetogenic effect of statins regarding their action on pancreatic  $\beta$ -cells, and cited in vitro studies showing that cholesterol excess in pancreatic  $\beta$ -cells impaired their function, proliferation, and survival, while cholesterol efflux improved both biological functions and the survival of  $\beta$ -cells. These effects depend on the LDL receptor-mediated cellular cholesterol entry [21].

This explanation of a reduced insulin secretion is also indirectly indicated by in vivo observations. A study using Mendelian randomisation showed that the effect of statins on the risk of incident diabetes depended on the reduction



of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase activity [22]. This is associated with an increase in LDL receptor activity. The tested single nucleotide polymorphisms in the HMG-CoA gene, i.e. rs17238484-G and rs12916, were selected based on genetic associations with reduced HMG-CoA reductase activity and lower LDL-C levels. Both polymorphisms were evaluated in a large population for their association, among others, with the risk of diabetes. The results showed that reduced HMG-CoA reductase activity was associated with a slightly increased risk of diabetes, with the odds ratio values of 1.02 (95% CI 1.00–1.05) for the rs17238484-G allele and 1.06 (95% CI 1.03–1.09) for the rs12916 allele. These associations may suggest that the risk of incident diabetes in statin users depends on the degree of HMG-CoA reductase activity inhibition, and thus the potency of a given statin.

The subsequent increase in LDL receptor activity may be the reason for cholesterol accumulation in  $\beta$ -cells and their dysfunction. This may be also indirectly indicated by a study in newly diagnosed patients with familial hypercholesterolaemia (FH) [23]. In this study, patients were categorised depending on the degree of LDL receptor activity reduction due to mutations leading to defective or absent receptors. The third group were patients with apolipoprotein B (apo B) gene mutation. The aim of the study was to evaluate whether the reduced incidence of diabetes type 2 in FH is due to reduced cholesterol uptake by pancreatic  $\beta$ -cells. The presence of type 2 diabetes was patient-reported. The prevalence of type 2 diabetes was 1.75% in patients with FH and 2.93% in healthy relatives (OR 0.62, 95% CI 0.55–0.69,  $p < 0.001$ ). The lowest rate was noted in patients with absent LDL receptors (null LDL-R), followed by those with defective receptors and patients with apo B gene mutation, with the respective odds ratios of 0.38 (95% CI 0.29–0.49), 0.49 (95% CI 0.40–0.60), and 0.65 (95% CI 0.48–0.87). Thus, the authors observed a reverse dose-response relationship between the severity of FH and the prevalence of type 2 diabetes.

A recent study by Spanish authors [24] is discordant with the above results by Besseling et al. [23]. The aim of the Spanish study was to evaluate the incidence of type 2 diabetes in patients with heterozygous FH (based on the National Dyslipidaemia Registry of the Spanish Atherosclerosis Society) and the effect of LDL-C level and the presence of FH-causative mutations on the risk of type 2 diabetes in these patients. Although the rate of incident type 2 diabetes was lower in patients with heterozygous FH compared to the general population, neither LDL-C level nor genetic mutations were risk factors for diabetes. The risk of diabetes was related to male sex, age, BMI, hypertension, baseline triglyceride levels, and duration of statin therapy in years.

Regardless of these findings, our current understanding of this issue seems to favour the hypothesis that statin-induced reduction of insulin secretion is associated with inhibition

of HMG-CoA reductase activity and subsequent increase in LDL receptor activity in pancreatic  $\beta$ -cells, leading to cellular cholesterol accumulation.

### *Insulin resistance*

Statins affect glucose metabolism by inhibiting its uptake in human adipose tissue cells, skeletal muscle cells, and pancreatic islet  $\beta$ -cells by inhibiting glucose transporter (GLUT) expression. This effect (reduction of GLUT4) was observed in adipocytes for simvastatin and atorvastatin [25, 26]. Atorvastatin, pravastatin, and rosuvastatin inhibited GLUT4 in skeletal muscle cells, and the first two statins decreased GLUT2 expression in islet  $\beta$ -cells [27].

It is also worth mentioning that statins decrease glucose uptake in several tumour lines, but they “do not inhibit expression of GLUT proteins, and their influence on glucose transport can be reversed by cholesterol biosynthesis pathway (mevalonic acid or farnesyl pyrophosphate)” [28]. This means that impaired glucose uptake resulted from the inhibition of cholesterol synthesis, and that it can be independent of glucose transporters.

Statin-induced HMG-CoA reductase inhibition leads to a reduced synthesis of not only cholesterol but also coenzyme Q10, which plays an important role in GLUT4 generation. Thus, inhibition of coenzyme Q10 may contribute to a reduced expression of this glucose transporter in adipocytes, leading to reduced glucose uptake, as indicated by the data showing that the addition of coenzyme Q10 improves simvastatin-induced reduction of GLUT4 expression [26]. In fact, inhibition of coenzyme Q10 plays a role not only in insulin resistance but also in inhibition of insulin secretion by a reduction in the production of adenosine triphosphate [29].

A decrease in adiponectin level might also link statin therapy to insulin resistance and incident diabetes [29]. Adiponectin levels show a negative correlation with abdominal obesity and insulin resistance [30], and high adiponectin levels are associated with a much lower risk of diabetes [31]. Proposed molecular mechanisms of the effect of adiponectin on insulin sensitivity include inhibition of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, and stimulation of glucose uptake and fatty acid oxidation in the skeletal muscle [30, 32]. In addition, reduced adiponectin level may have a negative effect not only on insulin sensitivity but also on insulin secretion [29]. However, the role of adiponectin in the pathomechanism of the diabetogenic effect of statins has not been clearly established.

As mentioned above, it is difficult to provide a consistent and comprehensive explanation of the complicated mechanisms of statin-induced development of diabetes because available data are still scarce. For a thorough review of some of these data, interested readers may be referred to recent papers by Lee et al. [4], Betteridge and Carmena [21], Chan et al. [29], and Mach et al. [33].

## STATINS AND CONTROL OF DIABETES

Ergou et al. [34] performed a meta-analysis of randomised statin clinical trials in patients with diabetes to evaluate the effect of statins on diabetes control. The meta-analysis included nine clinical trials (9696 participants) that provided data on HbA1c levels before and after the intervention. The mean duration of follow-up was 3.6 years. The mean HbA1c level was higher in statin users compared to controls (either placebo or standard therapy). The mean difference was 0.12% (0.04%–0.20%) or 1.3 mmol/L (0.4–2.2 mmol/L) ( $p = 0.003$ ).

A meta-analysis by Cai et al. [35], which included 36 studies with 6875 diabetic patients, showed an adverse effect of intensive LDL-C level reduction on HbA1c level. The mean difference in HbA1c level versus placebo was 0.37% (95% CI 0.19–0.55) in patients with the achieved LDL-C level  $\leq 1.8$  mmol/L and 0.08% (95% CI 0.02–0.14) in those with the achieved LDL-C level  $< 2.6$  mmol/L. In addition, intensive statin therapy resulted in a significant increase in HbA1c level.

## SUMMARY

Observational studies and randomised clinical trials indicate that statins induce diabetes. This effect is stronger with more intensive statin therapy (statin potency and dose), higher LDL-C level reduction, and lower target LDL-C level. The diabetogenic effect of statins is also related to the presence of risk factors for diabetes, such as components of metabolic syndrome. It should be stressed, however, that the benefits of statins in terms of cardiovascular risk reduction outweigh any harm related to their diabetogenic effect. Thus, statins should be continued in all patients in whom these drugs are indicated due to high or very high cardiovascular risk, despite the risk of diabetes development or worsening of diabetes control, and these patients should be treated until they achieve the target LDL-C levels.

Before initiation of statin therapy the risk of diabetes should be assessed [1, 36, 37]. Statin-treated patients at high risk of developing diabetes should be monitored for changes in blood glucose and HbA1c levels, and preventive lifestyle modification should be introduced. If diabetes develops, it should be managed according to the guidelines.

**Conflict of interest:** none declared

## References

- Maki KC, Diwadkar-Navsariwala V, Kramer MW. Statin use and risk for type 2 diabetes: what clinicians should know. *Postgrad Med.* 2018; 130(2): 166–172, doi: [10.1080/00325481.2018.1402658](https://doi.org/10.1080/00325481.2018.1402658), indexed in Pubmed: 29139315.
- Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med.* 2012; 172(2): 144–152, doi: [10.1001/archinternmed.2011.625](https://doi.org/10.1001/archinternmed.2011.625), indexed in Pubmed: 22231607.
- Cederberg H, Stančáková A, Yaluri N, et al. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia.* 2015; 58(5): 1109–1117, doi: [10.1007/s00125-015-3528-5](https://doi.org/10.1007/s00125-015-3528-5), indexed in Pubmed: 25754552.
- Lee J, Noh Y, Shin S, et al. Impact of statins on risk of new onset diabetes mellitus: a population-based cohort study using the Korean National Health Insurance claims database. *Ther Clin Risk Manag.* 2016; 12: 1533–1543, doi: [10.2147/TCRM.S117150](https://doi.org/10.2147/TCRM.S117150), indexed in Pubmed: 27785041.
- Jones M, Tett S, Peeters GM, et al. New-Onset Diabetes After Statin Exposure in Elderly Women: The Australian Longitudinal Study on Women's Health. *Drugs Aging.* 2017; 34(3): 203–209, doi: [10.1007/s40266-017-0435-0](https://doi.org/10.1007/s40266-017-0435-0), indexed in Pubmed: 28138911.
- Casula M, Mozzanica F, Scotti L, et al. Statin use and risk of new-onset diabetes: A meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis.* 2017; 27(5): 396–406, doi: [10.1016/j.numecd.2017.03.001](https://doi.org/10.1016/j.numecd.2017.03.001), indexed in Pubmed: 28416099.
- Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet.* 2012; 380(9841): 565–571, doi: [10.1016/S0140-6736\(12\)61190-8](https://doi.org/10.1016/S0140-6736(12)61190-8), indexed in Pubmed: 22883507.
- Crandall JP, Mather K, Rajpathak SN, et al. Statin use and risk of developing diabetes: results from the Diabetes Prevention Program. *BMJ Open Diabetes Res Care.* 2017; 5(1): e000438, doi: [10.1136/bmjdr-2017-000438](https://doi.org/10.1136/bmjdr-2017-000438), indexed in Pubmed: 29081977.
- Agarwala A, Kulkarni S, Maddox T. The association of statin therapy with incident diabetes: evidence, mechanisms, and recommendations. *Curr Cardiol Rep.* 2018; 20(7): 50, doi: [10.1007/s11886-018-0995-6](https://doi.org/10.1007/s11886-018-0995-6), indexed in Pubmed: 29779165.
- Rajpathak SN, Kumbhani DJ, Crandall J, et al. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care.* 2009; 32(10): 1924–1929, doi: [10.2337/dc09-0738](https://doi.org/10.2337/dc09-0738), indexed in Pubmed: 19794004.
- Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet.* 2010; 375(9716): 735–742, doi: [10.1016/S0140-6736\(09\)61965-6](https://doi.org/10.1016/S0140-6736(09)61965-6), indexed in Pubmed: 20167359.
- Mills EJ, Wu P, Chong G, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM.* 2011; 104(2): 109–124, doi: [10.1093/qjmed/hcq165](https://doi.org/10.1093/qjmed/hcq165), indexed in Pubmed: 20934984.
- Alberton M, Wu P, Druyts E, et al. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. *QJM.* 2012; 105(2): 145–157, doi: [10.1093/qjmed/hcr158](https://doi.org/10.1093/qjmed/hcr158), indexed in Pubmed: 21920996.
- Navarese EP, Buffon A, Andreotti F, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. *Am J Cardiol.* 2013; 111(8): 1123–1130, doi: [10.1016/j.amjcard.2012.12.037](https://doi.org/10.1016/j.amjcard.2012.12.037), indexed in Pubmed: 23352266.
- Thakker D, Nair S, Pagada A, et al. Statin use and the risk of developing diabetes: a network meta-analysis. *Pharmacoepidemiol Drug Saf.* 2016; 25(10): 1131–1149, doi: [10.1002/pds.4020](https://doi.org/10.1002/pds.4020), indexed in Pubmed: 27277934.
- Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA.* 2011; 305(24): 2556–2564, doi: [10.1001/jama.2011.860](https://doi.org/10.1001/jama.2011.860), indexed in Pubmed: 21693744.
- Waters DD, Ho JE, Boekholdt SM, et al. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. *J Am Coll Cardiol.* 2013; 61(2): 148–152, doi: [10.1016/j.jacc.2012.09.042](https://doi.org/10.1016/j.jacc.2012.09.042), indexed in Pubmed: 23219296.
- Corrao G, Monzio Compagnoni M, Rea F, et al. Clinical significance of diabetes likely induced by statins: Evidence from a large

- population-based cohort. *Diabetes Res Clin Pract.* 2017; 133: 60–68, doi: [10.1016/j.diabres.2017.08.008](https://doi.org/10.1016/j.diabres.2017.08.008), indexed in Pubmed: [28892732](https://pubmed.ncbi.nlm.nih.gov/28892732/).
19. Wang S, Cai R, Yuan Y, et al. Association between reductions in low-density lipoprotein cholesterol with statin therapy and the risk of new-onset diabetes: a meta-analysis. *Sci Rep.* 2017; 7: 39982, doi: [10.1038/srep39982](https://doi.org/10.1038/srep39982), indexed in Pubmed: [28071756](https://pubmed.ncbi.nlm.nih.gov/28071756/).
  20. Cai R, Yuan Y, Zhou Yi, et al. Lower intensified target LDL-c level of statin therapy results in a higher risk of incident diabetes: a meta-analysis. *PLoS One.* 2014; 9(8): e104922, doi: [10.1371/journal.pone.0104922](https://doi.org/10.1371/journal.pone.0104922), indexed in Pubmed: [25122464](https://pubmed.ncbi.nlm.nih.gov/25122464/).
  21. Betteridge DJ, Carmena R. The diabetogenic action of statins: mechanisms and clinical implications. *Nat Rev Endocrinol.* 2016; 12(2): 99–110, doi: [10.1038/nrendo.2015.194](https://doi.org/10.1038/nrendo.2015.194), indexed in Pubmed: [26668119](https://pubmed.ncbi.nlm.nih.gov/26668119/).
  22. Swerdlow DI, Preiss D, Kuchenbaecker KB, et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet.* 2015; 385(9965): 351–361, doi: [10.1016/S0140-6736\(14\)61183-1](https://doi.org/10.1016/S0140-6736(14)61183-1), indexed in Pubmed: [25262344](https://pubmed.ncbi.nlm.nih.gov/25262344/).
  23. Besseling J, Kastelein JJP, Defesche JC, et al. Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. *JAMA.* 2015; 313(10): 1029–1036, doi: [10.1001/jama.2015.1206](https://doi.org/10.1001/jama.2015.1206), indexed in Pubmed: [25756439](https://pubmed.ncbi.nlm.nih.gov/25756439/).
  24. Climent E, Pérez-Calahorra S, Marco-Benedí V, et al. Effect of LDL cholesterol, statins and presence of mutations on the prevalence of type 2 diabetes in heterozygous familial hypercholesterolemia. *Sci Rep.* 2017; 7(1): 5596, doi: [10.1038/s41598-017-06101-6](https://doi.org/10.1038/s41598-017-06101-6), indexed in Pubmed: [28717233](https://pubmed.ncbi.nlm.nih.gov/28717233/).
  25. Nakata M, Nagasaka S, Kusaka I, et al. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. *Diabetologia.* 2006; 49(8): 1881–1892, doi: [10.1007/s00125-006-0269-5](https://doi.org/10.1007/s00125-006-0269-5), indexed in Pubmed: [16685502](https://pubmed.ncbi.nlm.nih.gov/16685502/).
  26. 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(4): 251–255, doi: [10.1089/met.2012.0177](https://doi.org/10.1089/met.2012.0177), indexed in Pubmed: [23496027](https://pubmed.ncbi.nlm.nih.gov/23496027/).
  27. Zhao W, Zhao SP. Different effects of statins on induction of diabetes mellitus: an experimental study. *Drug Des Devel Ther.* 2015; 9: 6211–6223, doi: [10.2147/DDDT.S87979](https://doi.org/10.2147/DDDT.S87979), indexed in Pubmed: [26648697](https://pubmed.ncbi.nlm.nih.gov/26648697/).
  28. Malenda A, Skrobanska A, Issat T, et al. Statins impair glucose uptake in tumor cells. *Neoplasia.* 2012; 14(4): 311–323, doi: [10.1593/neo.12444](https://doi.org/10.1593/neo.12444), indexed in Pubmed: [22577346](https://pubmed.ncbi.nlm.nih.gov/22577346/).
  29. Chan DC, Pang J, Watts GF. Pathogenesis and management of the diabetogenic effect of statins: a role for adiponectin and coenzyme Q10? *Curr Atheroscler Rep.* 2015; 17(1): 472, doi: [10.1007/s11883-014-0472-7](https://doi.org/10.1007/s11883-014-0472-7), indexed in Pubmed: [25398645](https://pubmed.ncbi.nlm.nih.gov/25398645/).
  30. Kadowaki T, Yamauchi T, Kubota N, et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest.* 2006; 116(7): 1784–1792, doi: [10.1172/JCI29126](https://doi.org/10.1172/JCI29126), indexed in Pubmed: [16823476](https://pubmed.ncbi.nlm.nih.gov/16823476/).
  31. Li S, Shin HJ, Ding EL, et al. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA.* 2009; 302(2): 179–188, doi: [10.1001/jama.2009.976](https://doi.org/10.1001/jama.2009.976), indexed in Pubmed: [19584347](https://pubmed.ncbi.nlm.nih.gov/19584347/).
  32. Rabe K, Lehrke M, Parhofer KG, et al. Adipokines and insulin resistance. *Mol Med.* 2008; 14: 741–751, doi: [10.2119/2008-00058](https://doi.org/10.2119/2008-00058).
  33. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence — focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J.* 2018; 39(27): 2526–2536, doi: [10.1093/eurheartj/ehy182](https://doi.org/10.1093/eurheartj/ehy182), indexed in Pubmed: [29718253](https://pubmed.ncbi.nlm.nih.gov/29718253/).
  34. Erqou S, Lee C, Adler A. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. *Diabetologia.* 2014; 57(12): 2444–2452, doi: [10.1007/s00125-014-3374-x](https://doi.org/10.1007/s00125-014-3374-x).
  35. Cai R, Yuan Y, Sun J, et al. Statins worsen glycaemic control of T2DM in target LDL-c level and LDL-c reduction dependent manners: a meta-analysis. *Expert Opin Pharmacother.* 2016; 17(14): 1839–1849, doi: [10.1080/14656566.2016.1220539](https://doi.org/10.1080/14656566.2016.1220539), indexed in Pubmed: [27488607](https://pubmed.ncbi.nlm.nih.gov/27488607/).
  36. Sattar NA, Ginsberg H, Ray K, et al. The use of statins in people at risk of developing diabetes mellitus: evidence and guidance for clinical practice. *Atheroscler Suppl.* 2014; 15(1): 1–15, doi: [10.1016/j.atherosclerosissup.2014.04.001](https://doi.org/10.1016/j.atherosclerosissup.2014.04.001), indexed in Pubmed: [24840509](https://pubmed.ncbi.nlm.nih.gov/24840509/).
  37. Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J.* 2013; 34(39): 3035–3087, doi: [10.1093/eurheartj/eh108](https://doi.org/10.1093/eurheartj/eh108), indexed in Pubmed: [23996285](https://pubmed.ncbi.nlm.nih.gov/23996285/).

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