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

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

Brief title: Are statins diabetogenic?

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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 diabetes type 2 is associated with statin potency and dose. It seems also to be stronger if lowering effect is higher and LDL cholesterol level achieved is lower. The mechanisms of diabetes development in statin-treated patients are not completely understood. Generally, the increased insulin resistance and decrease insulin secretion are taken into account. However it should be kept in mind that statin cardiovascular risk reduction effect outweighs the harm related to diabetes induction. The patients at risk of diabetes development should be monitored, as regard the parameters of glucose metabolism, and preventive lifestyle measurements are recommended to be introduced. The new-onset diabetes should be managed according to the guidelines.

Key words: statins; diabetogenic effect; observational studies; randomised trials; mechanisms; recommendations
INTRODUCTION

Observational studies (1-6), randomized 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). The interest in this issue dates 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 been already in use for twenty 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 diabetes type 2 in statin users compared to non-users that was higher than in randomized 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 50-79 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 diabetes type 2 (HR 1.48, 95% Cl 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 45-73 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% Cl 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 hypoglycemic therapy during follow-up. Of note, this study was designed to evaluate the effect of statins on the risk of diabetes type 2 and not the risk of cardiovascular disease.
In a retrospective Korean population study, based on the Korean National Health Insurance registry, cases of new onset diabetes mellitus were evaluated in ischemic heart disease patients 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 diabetes type 2 was nearly twice more common among statin users (HR 1.84, 95% CI 1.63-2.09, adjusted for treatment intensity, individual drug, and co-morbidities). Regarding individual statins, atorvastatin, rosvastatin, simvastatin, and lovastatin use was associated with twofold higher diabetes risk. 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 hypoglycemic drugs.

Results of the observational Australian Longitudinal Study on Women’s Health, regarding incident diabetes cases in elderly women treated with statins, have been recently published (5). The analysis included 8372 Australian women aged 76-82 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.

Recently, Italian authors published a meta-analysis of observational studies to evaluate the association between statin use and the risk of new onset diabetes (6). Publications from 2004 to June 2016 were included, and the inclusion criteria for the meta-analysis were met by 18 observational studies and 2 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 rosvastatin 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 diabetes risk (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.
As mentioned above, the first study to indicate a diabetogenic effect of statins was the JUPITER study (7). It was a randomized 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 newly diagnosed diabetes type 2 cases 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 analyzed the rates of incident diabetes in relation to the presence of risk factors for diabetes. Four risk factors were taken into account, including metabolic syndrome, increased fasting glucose (100-125 mg/dL), body mass index (BMI) ≥30 kg/m² and HbA1c level >6%. In patients without risk factors for diabetes type 2 (n=6,095), diabetes 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=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 new diabetes cases, while 86 cardiovascular events were avoided without any new diabetes cases in patients with no risk factors for diabetes. Incident diabetes was physician-reported.

Recently, the results of a randomized 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 a high risk of diabetes (n=3,234). 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 diabetes risk (HR 1.36;
95% CI 1.17-1.58), and an increase in diabetes risk during statin treatment was noted in all three intervention groups. Diabetes diagnosis was 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 recently (9). To summarize, it could be said that in majority of the large randomized primary and secondary prevention trials involving different statins, with data available (respectively eight and five), no significant increase of relative ratio of new onset diabetes was observed. In two trials a positive association of statin treatment with incident diabetes was significant and in other the two there was no change. Only one primary prevention study found significant decrease of diabetes risk.

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

In 2009, Rajpathak et al. reported a meta-analysis of 6 clinical trials that included 57,593 patients (10). The mean duration of follow-up was 3.9 years. Statin use was associated with a 13% higher diabetes risk 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 4 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 4 years was associated with one incident diabetes case. In 2011, a meta-analysis of 76 randomized statin clinical trials was performed to evaluate the effect of these drugs on cardiovascular disease risk (12). Information on incident diabetes was provided in 17 trials. The increase in diabetes risk was the same as in the meta-analysis by Sattar et al. (OR 1.09, 95% CI 1.02-1.17). A year latter a meta-analysis of 72 randomized statin trials, done partly by the same authors, was conducted to evaluate adverse effects associated with statin use (13). Information on incident diabetes was provided in 16 of these trials. During the 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 4 trials) was associated with a significant 14% increase in the risk of diabetes (OR 1.14, 95% CI 1.01-1.29).

Another meta-analysis (2013) evaluated the effect of various statins and their doses on the risk of incident diabetes cases (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 diabetes risk (OR 1.15, 95% CI 0.90-1.50). Despite a trend for a higher diabetes risk 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 showed that a significant diabetes risk 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 (7 studies; OR 1.12, 95% CI 1.01-1.24).

Lipophilic statins were associated with a higher diabetes risk compared to placebo (OR 1.14, 95% CI 1.02-1.28). However, no increase in risk was noted in a head-to-head comparison with hydrophilic statins (OR 1.05, 95% CI 0.9-1.23).

**INTENSIVE VERSUS MODERATE INTENSITY STATIN THERAPY**

Although the some above studies also evaluated the effect of intensive statin therapy, versus moderate intensity treatment, on the risk of new-onset diabetes, studies are also available that specifically focused on this issue. These include meta-analyses by Preiss et al. (16) and Waters et al. (17). The former was a meta-analysis of 5 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 20-40 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 were also included in the analysis by Preiss et al. (16). However, this analysis also looked at the 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/m², 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 0-1 risk factors for diabetes (HR 0.97, 95% CI 0.77-1.22). In contrast, the risk of diabetes was increased in patients with 2-4 risk factors for diabetes (HR 1.24, 95% CI 1.08-1.42).

Reduction in the cardiovascular event rate with atorvastatin 80 mg per day, compared to moderate intensity treatment, was higher in both patient subgroups, i.e. with 0-1 or 2-4 risk factors for diabetes (HR 0.87, 95% CI 0.75-0.995; and HR 0.82, 95% CI 0.71-0.96, respectively). For one additional diabetes case, 204 patients with 2-4 risk factors for diabetes had to receive intensive atorvastatin therapy for one year, while 242 patients had to be treated to avoid one cardiovascular event.

**ASSOCIATION BETWEEN THE RISK OF INCIDENT DIABETES DURING STATIN THERAPY AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVEL REDUCTION**

This issue may be indirectly related to compliance to statin therapy, as evaluated in 84,828 residents of the Italian Lombardy region who were newly prescribed statin in 2003-2004 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 drugs.

Compared to very low compliance to 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 to statin therapy.

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

Meta-analyses have also been recently published that evaluated the association between low-density lipoprotein cholesterol (LDL-C) level reduction 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 8 studies with target LDL-C level <100 mg/dL or LDL-C level reduction by at least 30% and showed that the rate of incident diabetes during 4 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 20-30% compared to baseline, while the risk of diabetes was increased in patients with LDL-C level reduction by >30-40% and >40-50% (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 diabetes case was identified per 137 patients with LDL-C level reduction by 30-40% and 108 patients with LDL-C level reduction by 40-50%.

The association between statin therapy and the risk of incident diabetes was stronger in older patients, women, and in 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 that rate of new-onset diabetes during 4 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 ≤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 above mentioned METSIM study which showed that a 46% higher diabetes risk (HR 1.46, 95% CI 1.22-1.74) in statin users compared to non-users was accompanied by a 12% reduction of 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 a statin dose in patients treated with simvastatin or atorvastatin.

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

Reduced insulin secretion

Betteridge and Carmena discussed mechanisms of the diabetogenic effect of statins in regard to their action on pancreatic beta cells, citing in vitro studies that showed that cholesterol excess in pancreatic beta cells impaired their function, proliferation, and survival, while cholesterol efflux improved both biological functions and 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 randomization 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 rs17238848-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.

Subsequent increase in LDL receptor activity may be the reason for cholesterol accumulation in beta cells and dysfunction of the latter. This may be also indirectly indicated by a study in newly diagnosed patients with familial hypercholesterolemia (FH) (23). In this study, patients were categorized 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 diabetes type 2 was patient-reported. Diabetes type 2 was present in 1.75% of patients with FH compared to 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 diabetes type 2.

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 diabetes type 2 in patients with heterozygous FH (based on the National Dyslipidemia Registry of the Spanish Atherosclerosis Society) and the effect of LDL-C level and the presence of FH-causative mutations on the risk of diabetes type 2 in these patients. Although the rate of incident diabetes type 2 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 gender, 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 favor 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 β cells by inhibiting glucose transporters (GLUTs) expression. This effect (reduction of GLUT4) was observed in adipocytes for simvastatin and atorvastatin (25,26). Atorvastatin, pravastatin, rosuvastatin inhibited GLUT4 in skeletal muscle cells, and the first two statins decreased GLUT2 expression in islet β cells (27).

It is also worth mentioning that statins decrease glucose uptake in several tumor 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 also 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 a 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 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 ATP (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 diabetes risk (31). Proposed molecular mechanisms of the effect of adiponectin on insulin sensitivity include inhibition of hepatic neoglucogenesis, 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 as available data are still scanty. For a thorough review of some of these data, an interested reader 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. performed a meta-analysis of randomized statin clinical trials in patients with diabetes to evaluate the effect of statins on diabetes control (34). The meta-analysis included 9 clinical trials (9,696 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).

The meta-analysis by Cai et al. that included 36 studies with 6875 diabetic patients showed an adverse effect of intensive LDL-C level reduction on HbA1c level (35). 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 ≤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 randomized clinical trials indicate that statins induce diabetes. This effect is the stronger the more intensive is statin therapy (statin potency and dose), the higher is LDL-C level reduction, and the lower is target LDL-C level. The diabetogenic effect of statin is also related to the presence of risk factors for diabetes, such as components of the metabolic syndrome. It should be stressed, however, that the benefits of statins in terms of cardiovascular risk reduction outweigh any harms 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 developing or worsening of diabetes control, and these patients should be treated to 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 life style modification should be introduced. If diabetes develops, it should be managed according to the guidelines.
**Conflict of interest:** none declared

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