Review

Statins: Beneficial or Adverse for Glucose Metabolism

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Large-scale clinical trials have established that statin use for lowering blood cholesterol is beneficial in reducing atherosclerotic cardiovascular diseases in different populations. However, the general reputation of statins seems to be clouded by a potential adverse effect of a class of statins on glucose metabolism. This paper reviewed clinical data of statins regarding the effects on diabetes mellitus and glucose metabolism. At least five randomized controlled studies, primarily investigating the protective effect of statins on the risk of cardiovascular diseases, have addressed the effect of statins on glucose metabolism in Western countries. One study showed that pravastatin (40 mg/day) was protective against the development of diabetes mellitus. Two studies of atorvastatin (10 mg/day) and one study of simvastatin (40 mg/day) showed no measurable effect of these regimens on the risk of diabetes mellitus or the clinical course of diabetes mellitus. One study of atorvastatin (80 mg/day) versus pravastatin (40 mg/day) suggested a deterioration of glucose metabolism associated with a high dose of atorvastatin. In Japan, a few case reports have noted a potential adverse effect of atorvastatin on glycemic control in patients with diabetes mellitus; however, seven clinical trials have showed no such effect of atorvastatin although these studies were relatively small in size and short in follow-up. Only one of the two observational studies suggested a possible adverse effect of atorvastatin on glycemic control. Evidence is extremely limited regarding atorvastatin use and deterioration in glycemic control, and further studies are needed to draw a conclusion on this issue.


Key words: Pravastatin, Atorvastatin, Diabetes mellitus, Insulin, Blood glucose

Introduction

Statins, HMG-CoA reductase inhibitors, enhance the expression of low-density lipoprotein (LDL) receptors in the liver and consequently lower blood LDL cholesterol levels through inhibiting cholesterol synthesis in the liver. From large-scale clinical trials in different populations, it has been established that statin use substantially reduces the risk of cardiovascular diseases. In addition to lowering LDL cholesterol levels, statins are known to suppress the progression of atherosclerosis by their pleiotropic effects including the improvement of thrombus formation, antioxidant effect, improvement of vascular endothelial cell damage, anti-inflammatory action, and stabilization of plaques. Evidence from clinical trials has given statins the general reputation as very effective and safe cholesterol-lowering drugs, although adverse effects of statins, such as elevation of liver enzymes and rhabdomyolysis, are recognized. However, an incident of fatal rhabdomyolysis associated with cerivastatin raised a concern that the clinical efficacy and safety of statins may differ by the class of statins. Differences in the structural and physical properties of statins might result in the variation in pharmacokinetics, pleiotropic effects, and drug interactions.

It has been a matter of recent concern whether atorvastatin deteriorates diabetes mellitus or glycemic control. In 2003, immediately after the introduction of atorvastatin, two independent groups each reported two cases of diabetes mellitus showing deterioration in...
glycemic control during treatment with atorvastatin, and at least eight such cases were reported subsequently at meetings in Japan (Table 1). Very recently, a case of type 2 diabetes mellitus occurring after atorvastatin treatment was published. In this case, however, hyperglycemia, which was resolved with insulin therapy and discontinuation of atorvastatin, recurred with pravastatin use. As discussed in detail below, a sub-study of a multicenter randomized controlled trial, which was presented at the 2004 meeting of the American Heart Association (AHA), suggested that a high dose of atorvastatin (80 mg/day) might deteriorate glycemic control. In this paper, we review clinical data concerning the effects of statins on glucose metabolism, especially from the safety aspect, and discuss the possible mechanisms of these effects. For this task, we searched for relevant articles in PubMed with the combination of “Hydroxymethylglutaryl-CoA Reductase Inhibitors”[MeSH], “Clinical Trials”[MeSH] and “Diabetes Mellitus”[MeSH], and also the Japan Medical Abstracts Society web version 3 with a combination of key words (HMG-CoA reductase inhibitors, diabetes mellitus, proceedings, and human).

Table 1. Atorvastatin use and deterioration of blood glucose status in patients with diabetes mellitus: case reports presented at recent meetings in Japan

<table>
<thead>
<tr>
<th>Authors</th>
<th>Main findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katoh, et al.</td>
<td>Deteriorated HbA1c with ATR 5 mg for 1 month and with ATR 10 mg for 4 months (2 cases).</td>
<td>J Jpn Diab Soc, 48: 71, 2005</td>
</tr>
<tr>
<td>Kodera, et al.</td>
<td>Deteriorated non-fasting BS/HbA1c with ATR for 3-4 months (2 cases)</td>
<td>J Jpn Diab Soc, 48: 392, 2005</td>
</tr>
<tr>
<td>Seguchi, et al.</td>
<td>Deteriorated FBS/HbA1c with ATR for 3-6 months (3 cases)</td>
<td>J Jpn Diab Soc, 48: 392, 2005</td>
</tr>
<tr>
<td>Fukuniwa, et al.</td>
<td>Deteriorated HbA1c with ATR 5 mg for 2 months and then with PRV 10 mg for 2 months (1 case)</td>
<td>J Jpn Diab Soc, 48: 451, 2005</td>
</tr>
</tbody>
</table>

ATR: atorvastatin, BS: blood sugar, FBS: fasting blood sugar, PRV: pravastatin.

Based on the Japan Medical Abstracts Society web version 3 with a combination of key words (HMG-CoA reductase inhibitors, diabetes mellitus, proceedings, and human).

Randomized Controlled Trials in Western Countries

The effects of statins on the risk of diabetes mellitus or glycemic control have been directly addressed in at least five randomized controlled trials with the event of cardiovascular diseases as the primary endpoint. The West of Scotland Coronary Prevention Study was the first clinical trial which investigated the risk of diabetes mellitus associated with atorvastatin treatment. Originally, it was a double-blind trial in which 6,595 men aged 45-64 years with hypercholesterolemia but no evidence of cardiovascular disease were randomized to receive either pravastatin (40 mg/day) or placebo treatment. The subjects in the substudy were 5,974 men who had two or more post-randomization measurements of blood glucose and had neither self-reported diabetes nor fasting blood glucose of ≥ 7.0 mmol/L at baseline. The incidence of diabetes mellitus was defined as two glucose measurements of ≥ 7.0 mmol/L and at least one measurement of ≥ 2.0 mmol/L above the baseline level or newly started prescription of hypoglycemic drugs. During the follow-up period of 3.5-6.1 years, 139 became diabetic. After adjustment for body mass index, triglyceride, blood glucose, and other characteristics at baseline, the patients assigned to pravastatin therapy had a hazard ratio of 0.70 (95% confidence interval, 0.50-0.98) for transition to diabetes mellitus.

In the MRC/BHF Heart Protection Study, 20,536 subjects aged 40 to 80 years with and without diabetes mellitus were randomized to receive either simvastatin (40 mg/day) or placebo. The mean duration of follow-up was 4.8 years for participants with diabetes mellitus at entry and 5.0 years for those without. Among the 14,573 subjects without known diabetes mellitus at baseline, there was no difference in the incidence of diabetes mellitus defined as the initiation of oral hypoglycemic or insulin treatment or a specific report of new diabetes mellitus (4.6% in the simvastatin group and 4.0% in the placebo group, p = 0.10). Furthermore, among a random sample of 1,087 patients with diabetes mellitus at baseline, HbA1c levels slightly increased in both simvastatin (0.15%) and placebo (0.12%) groups during the study period, with no measurable difference between the
two \( (p = 0.8) \)^12.

In the Anglo-Scandinavian Cardiac Outcomes Trial\(^1\), 19,342 hypertensive patients aged 40 to 79 years were randomized to either of two antihypertensive regimens and 10,305 with non-fasting total cholesterol concentrations of 6.5 mmol/L or less were further randomized to either atorvastatin (10 mg/day) or placebo treatment. The median follow-up was 3.3 years. The occurrence of diabetes mellitus was prespecified as a tertiary endpoint. There was no difference in the development of diabetes mellitus between the atorvastatin and placebo treatments; the hazard ratio for atorvastatin versus placebo was 1.15 (95% confidence interval, 0.91 to 1.44).

In a substudy of the Pravastatin or Atorvastatin Evaluation in Myocardial Infarction (PROVE-IT) presented at the 2004 AHA meeting\(^8\), the effects of the two statins on glycemic control were evaluated. PROVE-IT was the first large-scale clinical study comparing two statins\(^1\). In this study, 4,162 patients were randomized to receive intensive lipid-lowering therapy with atorvastatin (80 mg/day) or standard lipid-lowering therapy with pravastatin (40 mg/day) immediately after the occurrence of acute coronary syndrome. As compared with patients treated with pravastatin, those with atorvastatin had a higher risk of developing HbA1c > 6.0% among those with baseline HbA1c ≤ 6.0% regardless of diabetes mellitus; the pooled hazard ratio was estimated to be 1.84 (95% confidence interval 1.52-2.22). This finding does not necessarily indicate that atorvastatin increases the risk of deterioration in glycemic control because the comparison was made against pravastatin treatment.

The Collaborative Atorvastatin Diabetes Study investigated the protective effect of atorvastatin (10 mg/day) versus placebo specifically on cardiovascular disease in 2,838 patients with type 2 diabetes mellitus\(^1\). No difference was noted between the two regimens with respect to changes in HbA1c levels and the therapeutic modality for diabetes mellitus. The mean HbA1c levels at the baseline were 7.9% in the atorvastatin group and 7.8% in the placebo group. The corresponding values after 4 years of follow-up were 8.3% and 8.1%, respectively. At the baseline, insulin was used in 19.7% of patients in the atorvastatin group and 18.9% of patients in the placebo group. These proportions had not changed significantly at the end of the follow-up period (atorvastatin 20.5% and placebo 18.2%).

In summary, one study showed that pravastatin (40 mg/day) was protective against the development of diabetes mellitus. Two studies of atorvastatin (10 mg/day) and one study of simvastatin (40 mg/day) showed no measurable effect of these regimens on the risk of diabetes mellitus or the clinical course of diabetes mellitus. One study of atorvastatin (80 mg/day) versus pravastatin (40 mg/day) suggested a deterioration of glucose metabolism associated with a high dose of atorvastatin. It should be noted that the onset or deterioration of diabetes mellitus was defined differently in the studies, however.

**Clinical Trials and Observational Studies in Japan**

None of the reported clinical trials regarding statins and cardiovascular diseases has been extended to examine the effects of statins on the risk of diabetes mellitus or glucose metabolism\(^1\). With hindsight, a possible adverse effect of atorvastatin on glucose metabolism was noted in a long-term one-arm trial of 287 patients with total cholesterol of \( \geq 220 \) mg/dL. The primary purpose of this trial was to investigate the efficacy of atorvastatin 5-10 mg/day on serum lipids\(^1\). The majority (81%) of the patients received atorvastatin 10 mg/day throughout the study period. The prescribed dose was changed from 10 mg/day to 20 mg/day in 7% of the patients, from 10 mg/day to 5 mg/day in 5%, and from 5 mg/day to 10 mg/day in 4%. The episode of a pre-specified abnormal elevation of fasting blood glucose was fairly frequently observed during the one-year period, as shown in Table 2. Furthermore, the grade of abnormal elevation was more severe for blood glucose than for other laboratory measurements. Sixteen laboratory tests were evaluated in terms of severity. The majority (82%) of the episodes of abnormal change in laboratory tests other than glucose were classified as grade 1 (slight deterioration), but 15 of the 21 episodes of abnormal elevation of blood glucose were classified as grade 2 (moderate deterioration) or grade 3 (severe deterioration). The abnormal elevation of Hba1c was also commonly seen during the study period. It should be noted that the abnormal elevation of blood glucose or HbA1c was evaluated in terms of the number of episodes rather than cumulative incident cases.

We identified 11 published studies examining changes in fasting blood glucose and/or HbA1c after treatment with a specific statin in diabetes patients (Table 3). Of these, three were randomized trials\(^1\), six were one-arm trials\(^1\), and two were retrospective, observational studies\(^1\). Except for three studies\(^1\), these studies were very small in size with fewer than 100 patients, and a relatively short follow-up period. None of the seven trials found any measurable adverse effect of atorvastatin on glycemic con-
Table 2. Episodes of abnormal laboratory tests occurring in hypercholesterolemic patients treated with atorvastatin 5-20 mg/day for one year

<table>
<thead>
<tr>
<th>Abnormal laboratory test</th>
<th>No. of patients</th>
<th>No. of episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation of gamma-glutamyltransferase</td>
<td>287</td>
<td>50 (17.4%)</td>
</tr>
<tr>
<td>Elevation of alanine aminotransferase</td>
<td>287</td>
<td>34 (11.8%)</td>
</tr>
<tr>
<td>Elevation of aspartate aminotransferase</td>
<td>287</td>
<td>26 (9.1%)</td>
</tr>
<tr>
<td>Elevation of fasting blood glucose</td>
<td>281</td>
<td>21 (7.5%)</td>
</tr>
<tr>
<td>Decreased testosterone</td>
<td>274</td>
<td>20 (7.3%)</td>
</tr>
<tr>
<td>Elevation of creatinine phosphokinase</td>
<td>287</td>
<td>19 (6.6%)</td>
</tr>
<tr>
<td>Elevation of choline esterase</td>
<td>287</td>
<td>16 (5.6%)</td>
</tr>
<tr>
<td>Elevation of HbA1c</td>
<td>282</td>
<td>15 (5.3%)</td>
</tr>
</tbody>
</table>

Derived from reference (15)

Table 3. Clinical trials and observational studies concerning statins and glycemic control in patients with diabetes mellitus in Japan

<table>
<thead>
<tr>
<th>Authors (ref.)</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Statin</th>
<th>Dose (mg/day)</th>
<th>Period</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanaka, et al.</td>
<td>RCT</td>
<td>40</td>
<td>Atorvastatin</td>
<td>10</td>
<td>12 weeks</td>
<td>No change in HbA1c for each group.</td>
</tr>
<tr>
<td>Endo, et al.</td>
<td>RCT</td>
<td>47</td>
<td>Atorvastatin</td>
<td>10</td>
<td>4 months</td>
<td>No change in HbA1c for each statin.</td>
</tr>
<tr>
<td>Kameda, et al.</td>
<td>RCT</td>
<td>14</td>
<td>Atorvastatin</td>
<td>10</td>
<td>9 months</td>
<td>No change in FBS/HbA1c for each drug.</td>
</tr>
<tr>
<td>Sato and Miyachi</td>
<td>One-arm trial</td>
<td>26</td>
<td>Atorvastatin</td>
<td>10-20</td>
<td>8 weeks</td>
<td>No change in HbA1c.</td>
</tr>
<tr>
<td>Hamano</td>
<td>One-arm trial</td>
<td>35</td>
<td>Atorvastatin</td>
<td>10</td>
<td>12 months</td>
<td>No change in FBS/HbA1c.</td>
</tr>
<tr>
<td>Sasamoto</td>
<td>One-arm trial</td>
<td>180</td>
<td>Atorvastatin</td>
<td>5-40</td>
<td>3-15 months</td>
<td>No change in FBS/HbA1c.</td>
</tr>
<tr>
<td>Suzuki</td>
<td>One-arm trial</td>
<td>160</td>
<td>Atorvastatin</td>
<td>10</td>
<td>3 months to 3 years</td>
<td>No change in HbA1c.</td>
</tr>
<tr>
<td>Yamada, et al.</td>
<td>One-arm trial</td>
<td>27</td>
<td>Pitavastatin</td>
<td>2</td>
<td>8 weeks</td>
<td>HbA1c increased by 0.17% (95% CI 0.01, 0.33).</td>
</tr>
<tr>
<td>Yamada</td>
<td>One-arm trial</td>
<td>57</td>
<td>Pitavastatin</td>
<td>1-2</td>
<td>30 months</td>
<td>No change in FBS.</td>
</tr>
<tr>
<td>Seino, et al.</td>
<td>Observational study</td>
<td>809</td>
<td>Pravastatin</td>
<td>5-20</td>
<td>3.9 years</td>
<td>No change in FBS/HbA1c for each statin.</td>
</tr>
<tr>
<td>Osaki, et al.</td>
<td>Observational study</td>
<td>67</td>
<td>Atorvastatin</td>
<td>10</td>
<td>2-3 months</td>
<td>Deteriorated HbA1c (≥ 10% relatively) was more frequent for atorvastatin (7/25, 28%) than pravastatin (3/42, 7%).</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial, FBS: fasting blood sugar.

trol\textsuperscript{17-23}. Only one observational study reported that deterioration of HbA1c was statistically significantly more frequent for atorvastatin than pravastatin\textsuperscript{27}, whereas the other observational study found no measurable change in fasting blood glucose or HbA1c in relation to atorvastatin and other statins\textsuperscript{26}. On the other hand, one of the two studies concerning pitavastatin showed a statistically significant increase in HbA1c after 8-week treatment\textsuperscript{24}. Findings from case reports may often signal an alarming adverse effect of a newly introduced drug, but they may sometimes be an extreme of random variation. One study graphically presented HbA1c values of 26 subjects before and after atorvastatin treatment\textsuperscript{20}. HbA1c increased markedly in a few individuals, and also decreased substantially in an almost equal number of subjects. Amelioration may not have been taken as seriously as deterioration in the routine clinical practice.

In summary, although the case reports suggested a potential adverse effect of atorvastatin in patients
Mechanisms of the Effects of Statins on Glucose Metabolism

Evidence is very limited as regards the mechanisms by which statins exert any influence on glucose metabolism. Statins may improve insulin resistance and be protective against glucose intolerance through their anti-inflammatory effects\(^\text{28, 29}\). Inflammatory markers have been related to an increased risk of diabetes mellitus in adults\(^\text{30, 31}\), and pro-inflammatory cytokines such as tumor necrosis factor (TNF)-\(\alpha\) are implicated as being linked with insulin resistance through their influence on insulin receptor\(^\text{32, 33}\). On the other hand, statins can deteriorate glycemic control by decreasing various metabolites, such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and ubiquinone (CoQ\(_{10}\)), which are normally produced during the process of cholesterol synthesis from acetyl CoA via mevalonic acid. Isoprenoid is known to enhance glucose uptake by upregulating the membrane transporter protein glucose transporter 4 (Glut 4), which plays a role in glucose uptake in adipocytes\(^\text{34}\). Suppressed biosynthesis of ubiquinone (CoQ\(_{10}\)), an essential factor in the electron-transfer system in mitochondria, may result in delayed ATP production in pancreatic \(\beta\) cells and thereby impair insulin release. It was recently shown that atorvastatin treatment resulted in a reduction of serum CoQ\(_{10}\) levels, which was positively correlated with LDL cholesterol levels\(^\text{35}\).

These mechanisms may differ by the property of statins. Water-soluble statins, such as pravastatin, are hepatocyte-specific and are not readily taken up by pancreatic cells and adipocytes. Lipid-soluble statins, such as simvastatin and atorvastatin, enter extrahepatic cells easily and may inhibit isoprenoid protein synthesis, consequently attenuating insulin action. Lovastatin, a lipid-soluble statin, was shown to down-regulate insulin-responsive Glut 4 and up-regulate Glut 1 in 3T3-L1 adipocytes leading to marked inhibition of insulin-stimulated glucose transport\(^\text{36}\). Another lipid-soluble statin, simvastatin, inhibited glucose-induced increase in intracellular Ca\(^{2+}\) of pancreatic \(\beta\) cells, leading to the inhibition of insulin secretion in a dose-dependent manner, while water-soluble pravastatin had absolutely no effect even at a high concentration of 100 \(\mu\)g/mL\(^\text{36}\). The inhibitory potency of HMG-CoA reductase and lipophilicity of statins may be related to different effects on glucose metabolism, although further studies are needed.

Conclusion

A few clinical studies have suggested that atorvastatin, especially at a high dose, may deteriorate glucose metabolism while pravastatin might improve glucose metabolism; however, evidence is extremely limited, and further studies are needed to draw a conclusion on this issue. The mechanisms by which these statins affect glucose metabolism also need to be studied further. The effect of statins on glucose metabolism, if any, seems particularly important in Japan. Japanese are more prone to developing diabetes mellitus than Caucasians\(^\text{37}\), and coronary risk is lower in Japan as compared with Western countries. A decreased risk of coronary artery disease conferred by statins well surpasses any adverse effect of intensive statin therapy in Western countries; however, it is uncertain whether such intensive statin therapy is also applicable in Japan.

References

6) Sica DA and Gehr TW: 3-Hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors and rhabdomyolysis: considerations in the renal failure patient. Curr Opin Nephrol


