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Statin Induced Diabetes

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Abstract: ***Statin drugs now carry a US Food and Drug Administration warning that they may increase the risk of diabetes mellitus and may worsen glycemic control in patients who already have diabetes. Meta-analyses indicate that statin therapy is associated with an increased risk for diabetes of approximately 9 %. The risk for incident diabetes may be associated with higher doses and potencies of statins. Mechanisms explaining the potentially higher incidence of type 2 diabetes with statin therapy have not been fully elucidated, and statins differ considerably in terms of their effect on glucose metabolism and ultimately incident diabetes. It is widely accepted that the cardiovascular benefits associated with statin use greatly outweigh the risks for diabetes. However, the effect of different statins on glycemic parameters may influence thechoice of statin in those with risk factors for diabetes. Unlike the other stains, pitavastatin raises adiponectin levels, which in turn lowers insulin resistance and improves insulin secretion. Furthermore, numerous studies have concluded that pitavastatin and pravastatin do not affect glycemic control and may be favorable treatment options in patients with, or at risk for, type 2 diabetes.***

Keywords: Statins, Cholesterol, Diabetes, Insulin resistance

1. Introduction

Statins are a class of medicines that are used to lower blood cholesterol levels. The drugs are able to block the action of a chemical in the liver that is necessary for making cholesterol. Though cholesterol is necessary for normal cell and body function, high levels of cholesterol can lead to atherosclerosis, a condition where cholesterol-containing plaques build up in arteries and block blood flow. By reducing blood cholesterol levels, statins lower the risk of chest pain (angina), heart attack, and stroke. Several types of statins exist such as atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin,rosuvastatin, and simvastatin.(1)

2. Statins Mechanism

Statins inhibit an enzyme called HMG-CoA reductase, which controls cholesterol production in the liver. The medicines actually act to replace the HMG-CoA that exists in the liver, thereby slowing down the cholesterol production process. Additional enzymes in the liver cell sense that cholesterol production has decreased and respond by creating a protein that leads to an increase in the production of LDL (low density lipoprotein, or "bad" cholesterol) receptors. These receptors relocate to the liver cell membranes and bind to passing LDL and VLDL (very low density lipoprotein). The LDL and VLDL then enter the liver and are digested.

Many people who begin statin treatment do so in order to lower their cholesterol level to less than 5 mmol/l, or by 25-30%. The dosage may be increased if this target is not reached. Treatment with the statin usually continues even after the target cholesterol level is reached in order to sustain atherosclerosis prevention.(1)

3. Statins and Diabetes

Some experimental studies support the hypothesis that statins may cause diabetes by altering glucose homeostasis through both impaired insulin secretion and diminished insulin sensitivity. Glucose is the most important signal for insulin release. Glucose is transported into the beta cells through glucose transporters 2 (GLUT2). Inside beta cells, glucose is phosphorylated to glucose-6-phosphate by enzyme glucokinase. Following further metabolic steps, adenosine triphosphate (ATP) is produced which closes ATP sensitive potassium channels. Resulting membrane depolarization leads to calcium influx through L-type calcium channels causing exocytosis of insulin containing granules. It has been reported that lipophilic statins(e.g., simvastatin) can inhibit glucose-induced cytosolic Ca 2+ signaling and insulin secretion by blocking L-type Ca 2+ channels in beta-cells and their inhibitory potencies parallel their lipophilicities.(2) During the process of cholesterol synthesis from acetyl CoA, various metabolites such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate and ubiquinone (Coenzyme Q10 [CoQ10]) are normally produced. Statins can reduce these metabolites which may affect insulin secretion or action adversely. For example, statins have been shown to reduce levels of CoQ10, which is a component of electron transport chain involved in the process of ATP generation.(3) Reduced levels of CoQ10 can result in delayed production of ATP and consequently diminish insulin release. Furthermore, inhibition of isoprenoid biosynthesis by statins has been implicated in downreguation of GLUT4 in adipocytes.(4) GLUT4 mediates insulin stimulated uptake of glucose in skeletal muscles and adipocytes. Atorvastatin and simvastatin have been shown to decrease the expression of GLUT4 in adipocytes which may result in impaired glucose tolerance.(5)(6) Adiponectin is an insulin sensitizing and anti-inflammatory cytokine released from adipocytes. Rosuvastatin and simvastatin have been shown to decrease plasma adiponectin levels and insulin sensitivity while pravastatin increased both.(7)(8)

Mitochondrial dysfunction in beta cells,(9) skeletal muscles (10) and adipocytes (11) has been linked with the pathogenesis of diabetes. Since statins are known to cause mitochondrial dysfunction in skeletal muscles, (12) it is plausible that similar mechanism is also responsible for their diabetogenic effect. In addition, statin induced myalgia and fatigue may impair exercise capacity and aggravate

sarcopenia, which is associated with glucose intolerance and type 2 diabetes.(13) Therefore, multiple mechanisms may lead to impairment of glycemic control and risk of NOD with statins. Further studies are needed to confirm these hypotheses.

Questions have been raised as to whether the type of statin used, the intensity of therapy, or the population studied contributed to these differences. Various studies suggest that factors such as using hydrophilic vs lipophilic statins, the dose, the extent of lowering of low-density lipoprotein cholesterol (LDL-C), and the age or clinical characteristics of the population studied may influence this relationship.(14)(15)(16)

Yamakawa et al, examined the effect of atorvastatin 10 mg/day, pravastatin 10 mg/day, and pitavastatin (Livalo) 2 mg/day on glycemic control over 3 months in a retrospective analysis. Random blood glucose and hemoglobin A1c levels were increased in the atorvastatin group but not in the other two.(14)

A prospective comparison of atorvastatin 20 mg vs pitavastatin 4 mg in patients with type 2 diabetes, presented at the American College of Cardiology's 2011 annual meeting, reported a significant increase in fasting glucose levels with atorvastatin, particularly in women, but not with pitavastatin.(15)

In the Compare the Effect of Rosuvastatin With Atorvastatin on Apo B/Apo A-1 Ratio in Patients With Type 2 Diabetes Mellitus and Dyslipidaemia (CORALL) study,(16) both highdoserosuvastatin (40 mg) and high-dose atorvastatin (80 mg) were associated with significant increases in hemoglobin A1c, although the mean fasting glucose levels were not significantly different at 18 weeks of therapy. A meta-analysis by Sattar et al (17) did not find a clear difference between lipophilic statins (OR 1.10 vs placebo) and hydrophilic statins (OR 1.08). In analysis by statin type, the combined rosuvastatin trials were statistically significant in favor of a higher diabetes risk (OR 1.18, 95% CI 1.04–1.44). Non significant trends were noted for atorvastatin trials (OR 1.14) and simvastatin trials (OR 1.11) and less so for pravastatin (OR 1.03); the OR for lovastatin was 0.98. This may suggest that there is a stronger effect with more potent statins or with greater lowering of LDL-C.

Meta-regression analysis in this study demonstrated that diabetes risk with statins was higher in older patients but was not influenced by body mass index or by the extent that LDL-C was lowered.

4. Clinical Considerations

As we eagerly wait for the results of trials addressing this question more directly, some steps which may help the physician to provide maximum protection from CVD to their patients, at the same time avoiding NOD are as follows.(18)Reports suggest that statins are being prescribed without good evidence.(19) They should be used based on clear therapeutic rationale and not considered to be magic bullets. Since intensive-dose therapy carries higher risk, treatment should be started with low doses. High dose statins are better avoided in women and elderly. Although not proven, pravastatin appears to reduce risk for NOD, while atorvastatin, rosuvastatin and simvastatin all significantly increase the risk. Benefits of regular exercise and dietary modifications should be stressed at every contact with the patient. It will be wise to inform patients about the possible risk of NOD with statin use since it will make them more compliant with lifestyle modifications and at the same time prevent the health care provider from any legal disputes later. Before starting statin therapy, screening for type 2 diabetes may be considered. All patients on intensive-dose statin therapy should be regularly monitored using fasting glucose level and HbA1c.Vitamin D deficiency has been linked with insulin resistance (20) and supplementation of vitamin D has been shown to improve insulin sensitivity. Patients on statin therapy may be screened for vitamin D deficiency and treated accordingly.

5. Conclusion

Statins are now used with the understanding that a slightly increased risk for diabetes is outweighed by the CV benefits. However, the differential metabolic effects of the various statins should be taken into account when deciding treatment plans for patients with a high risk for developing diabetes. Based on meta-analyses, pravastatin is considered the statin with the least risk for incident diabetes; however, pitavastatin consistently shows neutral to beneficial effects on glycemic parameters similar to that of pravastatin, and has shown superior lipid-lowering ability compared with pravastatin. In comparative studies, pitavastatin has demonstrated a favorable effect on glycemic parameters compared with other statins. Further data are needed to confirm these findings and assess their relevance to clinical outcomes.

References

[1] What are statins? How statins work and the side eefects of statins; Peter CrostaM.A; Medical news today.
[2] Yada T, Nakata M, Shiraishi T, Kakei M. Inhibition by simvastatin, but not pravastatin, of glucose-induced cytosolic Ca2+signalling and insulin secretion due to blockade of L-type Ca2+channels in rat islet beta-cells. Br J Pharmacol1999;126:1205-13
[3] Mabuchi H, Higashikata T, Kawashiri M, Katsuda S, Mizuno M, Nohara A, et al. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. J Atheroscler Thromb 2005;12:111-9.
[4] Chamberlain LH. Inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes. FEBS Lett 2001;507:357-61.
[5] Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): Implications in glycaemic control. Diabetologia 2006;49:1881-92
[6] Ganesan S, Ito MK. Coenzyme Q10 ameliorates the reduction in GLUT4 transporter expression induced by simvastatin in 3T3-L1 adipocytes. Metab SyndrRelat Disord 2013;11:251-5.

[7] Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Park JB, et al. Differential metabolic effects of pravastatin and simvastatin in hypercholesterolemic patients. Atherosclerosis 2009;204:483-90.
[8] Koh KK, Quon MJ, Sakuma I, Han SH, Choi H, Lee K, et al. Differential metabolic effects of rosuvastatin and pravastatin in hypercholesterolemic patients. Int J Cardiol 2013;166:509-15.
[9] Supale S, Li N, Brun T, Maechler P. Mitochondrial dysfunction in pancreatic β cells. Trends Endocrinol Metab 2012;23:477-87
[10] Phielix E, Mensink M. Type 2 diabetes mellitus and skeletal muscle metabolic function. Physiol Behav 2008;94:252-8
[11] Wang CH, Wang CC, Huang HC, Wei YH. Mitochondrial dysfunction leads to impairment of insulin sensitivity and adiponectin secretion in adipocytes. FEBS J 2013;280:1039-50.
[12] Sirvent P, Fabre O, Bordenave S, Hillaire-Buys D, Raynaud De Mauverger E, Lacampagne A, et al. Muscle mitochondrial metabolism and calcium signaling impairment in patients treated with statins. Toxicol Appl Pharmacol2012;259:263-8.
[13] Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: Findings from the National Health and Nutrition Examination Survey III. PLoS One 2010;5:e10805.
[14] Yamakawa T, Takano T, Tanaka S, Kadonosono K, Terauchi Y. Influence of pitavastatin on glucose tolerance in patients with type 2 diabetes mellitus. J Atheroscler Thromb 2008; 15:269–275.
[15] Barzilay JI, Davis BR, Pressel SL, et al; ALLHAT Collaborative Research Group. Long-term effects of incident diabetes mellitus on cardiovascular outcomes in people treated for hypertension: the ALLHAT Diabetes Extension Study. Circ Cardiovasc Qual Outcomes 2012; 5:153–162.
[16] Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372:1231–1239.
[17] Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375:735–742.
[18] Ummie Aiman;Ahmed najmi;Rahat Ali Khan; Statin induced diabetes and its clinical implications;volume-5;2014;181-185.
[19] Johansen ME, Gold KJ, Sen A, Arato N, Green LA. A national survey of the treatment of hyperlipidemia in primary prevention. JAMA Intern Med 2013;173:586-8.
[20] Alvarez JA, Ashraf A. Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. Int J Endocrinol 2010;2010:35138