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REVIEW

Impact of lipid-lowering therapy on glycemic control and the risk for new-onset diabetes mellitus

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Abstract

Lipid-lowering therapy is used very commonly nowadays not only for the optimization of the lipid profile but also to reduce cardiovascular risk. However, some studies have linked the use of certain lipid-lowering agents with an increased risk for impaired glycemic control and new-onset diabetes mellitus, a condition well established as an important risk factor for cardiovascular disease. On the other hand, some other lipid-lowering agents have been shown to have a beneficial effect on glucose metabolism. Profound knowledge of these differences would enable the clinician to choose the right lipid-lowering medication for each individual patient, so that the benefits would outweigh the risk of side effects. This review aims to present and discuss the clinical and scientific data pertaining to the impact of lipid-lowering therapy on glycemic control and the risk for new-onset diabetes mellitus.

Keywords: cardiovascular risk, diabetes mellitus, glycemic control, lipid-lowering.

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Introduction

Lipid-lowering therapy is used very commonly nowadays not only for the optimization of the lipid profile but also to reduce cardiovascular risk.[1–3] However, some studies have linked the use of certain lipid-lowering agents with an increased risk for impaired glycemic control and new-onset diabetes mellitus, a condition well established as an important risk factor for cardiovascular disease.[4,5] On the other hand, certain other lipid-lowering agents may actually improve glucose metabolism.

This review aims to present and discuss the clinical and scientific data pertaining to the impact of lipid-lowering therapy on glycemic control and the risk for new-onset diabetes mellitus. Thus, we conducted a PubMed search until September 2018 through the English literature using the search terms referring to the different classes of the lipid-lowering agents ('Bile acid sequestrants', 'Fibrates', 'Niacin', 'Ezetimibe', 'statins', 'PCSK9 inhibitors') in combination with the search term 'Diabetes'. We also included references from the articles identified and publications available in the authors' libraries.

Bile acid sequestrants

Bile acids are endogenous molecules synthesized in the liver from cholesterol and constitute the major pathway for fecal excretion of cholesterol. These molecules facilitate glucose metabolism, lipid homeostasis, lipid-soluble vitamin absorption, and energy metabolism through the activation of bile acid receptors in the gut, peripheral tissues, and liver. The two main bile acid receptors associated with the regulation of metabolism are the nuclear farnesoid X receptor (FXR) and the membrane-bound Takeda G protein coupled receptor 5 (TGR5). Both receptors play an important role in the development of metabolic disorders, such as diabetes and obesity.[6,7]

Bile acid sequestrants (BAS), such as colesevelam, cholestyramine, and colestipol, constitute a class of drugs that bind negatively charged bile acids in the intestinal lumen, leading to the formation of a nonabsorbable complex, which disrupts the enterohepatic circulation of bile acids, resulting in increased fecal excretion. The increased fecal excretion of bile acids promotes an increase in bile acid synthesis, resulting in the upregulation of low-density lipoprotein (LDL) receptors in the liver and, subsequently, decreased circulating levels of LDL cholesterol (LDL-C).[8,9]

BAS were initially developed with the purpose of treating hypercholesterolemia; however, current studies have shown improved glycemic control when used in diabetic patients.[10] Colesevelam, added to the antidiabetic regimen of patients with diabetes mellitus, demonstrated statistically significant reductions in glycosylated hemoglobin (HbA1c) by 0.5% and fasting plasma glucose (FPG) by an average of 15 mg/dL. Furthermore, colesevelam treatment was associated with reductions in the circulating levels of postprandial glucose and fructosamine.[11,12]

Even though the exact mechanism by which BAS improve glycemic control is not well understood, these lipid-lowering medications have been shown to increase circulating incretin hormones and to improve tissue glucose metabolism.[13]

Fibrates

These fenofibric acid derivatives exert their hypolipidemic effects primarily via the activation of peroxisome proliferator-activated receptor alpha (PPAR-α), a ligand-activated transcription factor that belongs to the steroid hormone receptors, which plays a central role in lipid and lipoprotein metabolism, resulting in a reduction of plasma triglyceride (TG) levels and an increase in high-density lipoprotein cholesterol (HDL-C) levels.[14,15]

In addition to their hypolipidemic effects, fibrates may contribute to the reduction of atherosclerosis progression and cardiovascular events and appear to have beneficial effects on diabetes-related microvascular diseases.[16]

Fibrates have not been associated with an increased risk of new onset diabetes mellitus. On the contrary, even though the mechanism is not well understood, fibrate therapy has been linked to a better glycemic control and improved insulin sensitivity.[16,17]

Niacin

Nicotinic acid (Niacin, Vitamin B3) is a water-soluble vitamin. It serves as a precursor for two essential coenzymes, nicotinamide adenine dinucleotide (NAD), and nicotinamide adenine dinucleotide phosphate (NADP), which participate in oxidation–reduction reactions and are essential in several metabolic processes.[18]

With regard to its use in the management of dyslipidemia, niacin decreases apo-B containing lipoproteins (LDL and very low-density lipoprotein [VLDL]) and increases apo A-1 containing lipoproteins (HDL). Studies also have shown that niacin directly inhibits hepatocyte diacylglycerol acyltransferase-2, an essential enzyme for the synthesis of TGs, and also has antioxidative, anti-inflammatory, and antiatherogenic properties.[19–21]

Unfortunately, niacin use has been associated with a rise in glucose levels, not only among patients with diabetes but also on normoglycemic individuals.[22,23] This effect is more prominent when niacin therapy is initiated or the dose is increased. Therefore, glucose control should be monitored very closely on initiating or increasing the dosage of niacin, especially in patients with diabetes.[24]

However, despite initial favorable results in patients with coronary artery disease (CAD),[25] in more recent trials, niacin, coadministered with statins, not only failed to reduce cardiovascular risk but was also associated with an increased risk of adverse events.[26,27] This led to a significant decrease in the use of niacin in current clinical practice.

Ezetimibe

Ezetimibe selectively reduces dietary and biliary cholesterol absorption by targeting the Niemann–Pick C1-like 1 (NPC1L1) protein at the hepatocytes and at the brush-border membrane of enterocytes. NPC1L1 mediates intestinal cholesterol absorption and hepatic biliary cholesterol secretion.[28,29]

Ezetimibe decreases LDL-C by approximately 18% and may also provide a modest reduction of TGs and a modest increase in HDL-C levels. It can be used as a monotherapy for the management of hypercholesterolemia but is more frequently used as an adjunct to statin therapy in high-risk patients who do not achieve the desired LDL-C goal with statin monotherapy.[30]

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL-C levels and improved cardiovascular outcomes.[31]

Ezetimibe does not increase fasting glucose levels,[32] and its use has been associated with an improved glucose metabolism in patients with insulin resistance.[33]

Statins

Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an essential enzyme in the cholesterol synthesis. Statins are the standard of care in the management of hypercholesterolemia in current clinical practice. Their effectiveness in LDL-C-lowering and in the reduction of cardiovascular risk in both primary and secondary prevention is indisputable.[34–39]

Besides their LDL-C-lowering properties, statins are now widely accepted to have anti-inflammatory effects, which significantly contribute to the reduction of cardiovascular risk.[40,41] However, the use of statins has been linked to an increased incidence of new-onset diabetes mellitus.

In a randomized, double-blind, placebo-controlled, multicenter trial (JUPITER trial), treatment with rosuvastatin was associated with a 25% increase in the incidence of physician-reported newly diagnosed diabetes.[41] In a meta-analysis, which included 57,593 patients with a mean follow-up of 3.9 years, statin use led to a 13% increase in the risk of diabetes.[42] In another large meta-analysis, which included 91,140 participants from 13

incorporated statin trials, statin therapy was associated with a 9% increase in the risk of incident diabetes.[43] A very large network meta-analysis, which included 29 trials with 163,039 participants, showed that statin use was associated with a 12% increase in the likelihood of developing diabetes. Atorvastatin 80 mg was associated with the highest increase in the risk of diabetes (34% increased risk), followed by rosuvastatin (17% increased risk).[44] In another meta-analysis, which included 20 studies of ≥1000 subjects, followed up for ≥1 year, statin use was associated with a 44% increase in the incidence of new-onset-diabetes mellitus. Estimates for all single statins showed a class effect, from rosuvastatin (61% increase in the incidence of new-onset-diabetes mellitus) to simvastatin (38% increase in the incidence of new-onset-diabetes mellitus).[45] In an analysis conducted to assess the association of statin use with diabetes mellitus using data from the Diabetes Prevention Program (DPP), it was shown that statin therapy raised the risk of incident diabetes by 36% in a cohort of overweight and obese individuals at high risk for diabetes, followed specifically for incident diabetes.[46] In a large study, which included 8749 nondiabetic subjects with a follow-up period of 5.9 years, after adjustment for confounding factors, it was shown that both simvastatin and atorvastatin increased the risk of type 2 diabetes mellitus by 49 and 21%, respectively, compared with no statin treatment. Furthermore, the effect of both simvastatin and atorvastatin on the risk of diabetes was dose-dependent.[47] In addition, there is also evidence suggesting that the positive association between statin use and diabetes was more pronounced with longer duration of statin therapy.[48]

The effect of statin therapy on glycemic control and the incidence of new-onset diabetes may differ depending on the specific statin used. In a very recent systematic review, which included 27,966 subjects from 37 clinical studies, rosuvastatin was shown to adversely affect glycemic control, and atorvastatin and simvastatin were also shown to negatively impact glycemic control in a dose-dependent manner. Furthermore, a time-dependent effect was also observed with atorvastatin use, which may also be present among other statins. Pitavastatin was also reported to be associated with a worsening of glycemic control, though to a lesser degree as compared with atorvastatin. On the other hand, pravastatin and fluvastatin appeared to exert a neutral or possibly favorable effect on glycemic control, although further studies are required to confirm this.[49]

The precise mechanisms for statin-induced diabetes mellitus remain unclear; however, several mechanisms have been proposed, including impaired insulin sensitivity, impaired insulin secretion, and compromised β cell function via enhanced intracellular cholesterol uptake due to inhibition of intracellular cholesterol synthesis by statins.[47,50]

Notwithstanding, it has to be stressed here that the cardiovascular benefits of statins far outweigh diabetes risk. In an analysis from the JUPITER trial, it was shown that in subjects with diabetes risk factors treated with rosuvastatin, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. On the other hand, in rosuvastatin-treated trial participants with no major diabetes risk factors, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed.[51]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

PCSK9 is a serine protease, which promotes the degradation of LDL receptors by targeting the receptors for lysosomal destruction. This results in a decreased rate of LDL-C clearance from circulation with subsequent elevation in serum LDL-C levels. Therefore, PCSK9 inhibitors, by preventing the degradation of LDL receptors by the enzyme PCSK9, induce a significant reduction in serum LDL-C concentration.[52]

When added to statin therapy, PCKS9 inhibitors have been shown to provide an incremental LDL-C reduction of approximately 60% and to significantly improve cardiovascular outcomes.[3,53]

With regard to glucose metabolism and risk of new-onset diabetes mellitus, there is some evidence from a mendelian randomization study indicating that certain genetic PCSK9 variants linked to lower LDL-C levels were also associated with higher FPG levels, bodyweight, and waist-to-hip ratio. In addition, these variants were also associated with a 29% increase in the risk of type 2 diabetes mellitus.[54,55]

However, in a prespecified analysis of the FOURIER trial,[56] which was conducted to investigate the efficacy and safety of evolocumab by diabetes status at baseline and the effect of evolocumab on glycemia and risk of developing diabetes, evolocumab did not increase the risk of new-onset diabetes in patients without diabetes at baseline (HR, 1.05; 95% CI: 0.94–1.17), including those with prediabetes (HR, 1.00; 95% CI: 0.89–1.13). Levels of HbA1c and FPG did not differ significantly over time between the evolocumab and placebo groups in patients with diabetes, prediabetes, or normoglycemia.[55,56] Furthermore, it was clearly shown that evolocumab significantly reduced cardiovascular risk in patients with and without diabetes at baseline.[55,56] In addition, there is also evidence from the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER-1) Extension Study that even longer use of evolocumab, up to 4 years, does not lead to an increase in the annualized incidence of new-onset diabetes mellitus after adjusting for duration of evolocumab exposure (4 versus 2.8% in the standard-of-care therapy alone group versus the evolocumab plus standard-of-care therapy group, respectively).[57]

On the other hand, in the ODYSSEY OUTCOMES trial, alirocumab did not also increase the risk of new-onset diabetes mellitus, nor did it worsen diabetic status in patients with pre-existing diabetes mellitus. More specifically, the incidence of new-onset diabetes mellitus was 9.6% in the alirocumab group versus 10.1% in the placebo group, whereas the incidence of diabetes worsening or diabetic complications in patients with pre-existing diabetes mellitus was 18.8% in the alirocumab group versus 21.2% in the placebo group.[53]

Given the above, the use of PCSK9 inhibitors appears to be associated with a substantial clinical benefit without adversely affecting glucose metabolism and without increasing the incidence of new-onset diabetes mellitus. However, further large studies with a long follow-up period will have to be conducted to confirm these findings before expanding the use of these agents.[58]

Conclusions

From the above clinical and scientific data, it becomes evident that the various classes of lipid-lowering agents have diverse effects on glucose metabolism and affect differently the risk of new-onset diabetes mellitus. Some lipid-lowering agents (e.g. statins) provide potent LDL-C-lowering but may increase the risk for new-onset diabetes mellitus. On the other hand, some other lipid-lowering agents (e.g. BAS) may provide an LDL-C reduction of a lesser magnitude but have a beneficial effect on glucose metabolism and cause a decrease in HbA1c. Profound knowledge of these differences would enable the clinician to choose the right lipid-lowering medication for each individual patient, so that the benefits would outweigh the risk of side effects.

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