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REVIEW ARTICLE

DIABETOGENIC EFFECT OF STATINS: MOLECULAR MECHANISMS

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ABSTRACT
Statins, HMG CoA inhibitors, are potent hypolipidemic drugs.They are used for the prevention of cardiovascular diseases and some of the most commonly used drugs worldwide. Long term statin therapy can cause a modest increase in new-onset diabetes risk, and there is great interest in the mechanisms for this adverse effect. Main proposed mechanisms are increased insulin resistance and some defects in insulin secretion. Many factors can affect the risk including pre-existing diabetic risk, older age and potency of statin. But clearly, the benefits of these drugs in preventing cardiovascular disease outweigh the potential risk of diabetes.The aim of this review is to give underlying pathomechanisms and clinical relevance of diabetogenic effect of statins.
Keywords: adverse effect, diabetogenicity, mechanism, risk, statins.

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INTRODUCTION

Cardiovascular disease (CVD) is an important cause of mortality, and hypercholesterolemia is the major CVD risk factor[1]. Statins (HMGCoA) reductase inhibitors were first approved by the FDA in 1987 and they are still the first-choice drugs for their potent hypocholesterolemic properties. Since then statins have become the most prescribed drugs worldwide[2,3]. They have also pleiotropic effects facilitating cardioprotective properties including benefits on endothelial function, decreasing inflammation and atherosclerotic plaque stabilization[4-8]. Other pleiotropic mechanisms of statins are improvement of bone diseases and central nervous system diseases[7]. On the other hand, despite well-known clinical benefit of statins on CV prevention, their possible adverse effects cannot be disregarded[9-11]. In addition increased in liver enzymes and development of myopathy[1], clinical trials show an increase in new-onset diabetes mellitus (NODM) by statin therapy, especially in the presence of diabetic risk factors, such as insulin resistance with impaired glucose control, obesity, metabolic syndrome, Asian ancestry, woman, elderly people, lower LDL(low density lipoprotein)-C levels, or large LDL-C reduction[10,12]. Data suggest a 10-22% increased risk of NODM comparing to nonusers. The risk increases with intensive treatment[13,14].While this is a drug class effect, recent data suggest that pravastatin and pitavastatin have no or week effects on glucose homeostasis[13].

Type 2 diabetes mellitus (T2DM) is a major risk factor for CV outcomes[15]. Statins are recommended and prescribed to diabetic patients to prevent CV complications[16]. The consensus of their benefits on CV risk reduction is more important than their adverse diabetogenic effect. Currently, on the market there are seven statin drugs: Atorvastatin, pitavastatin simvastatin fluvastatin, rosuvastatin, lovastatin and pravastatin.When they are classified, pravastatin and rosuvastatin are hydrophilic; atorvastatin, fluvastatin, lovastatin, pitavastatin and simvastatin are lipophilic statins. NODM risk was observed first in the JUPITER trial in 2008[17,18]. Then greater attention has been given to this issue, and by the time the risk has been supported by many trials[19-23]. In JUPITER study the risk was found to be increased with high statin doses and there were no new NODM cases among patients with no diabetes risk factors at baseline[24]. After the FDA evaluation, in March 2012, NODM risk warning was inserted to all statin packages[25]. The risk is limited to people with diabetes risk factors[26-28]. According to data, the risk of diabetes-induced complications, such as microvascular complications are not increased by statins.

The risk of NODM by different statins are arguable. Dormuthh *et al.*,[29] reported that higher potency statins can cause moderate risk increase compared with lower potency statins. It appears the risk is in parallel with their HMGCoA reductase inhibition capacity. It was suggested that lipophilic statins are more diabetogenic than the hydrophilic ones[9,29,31]. But recent clinical data have indicated that there is no difference between them regarding the risk of NODM[32]. Thus we need more data to determine potential differences among statins. Recent evidence suggests that pravastatin has week diabetogenic effect[33]. In a new cohort study, with moderate-intensity therapy, rosuvastatin was found to be less diabetogenic than pitavastatin[32].

Molecular mechanisms

Diabetogenic effect of statins reflect inhibition of HMGCoA reductase. Statins decrease synthesis of mevalonate products causing to impaired pancreatic β-cell function, but the exact mechanism(s) of diabetogenesis are still unclear[13]. It seems some defects on insulin release mechanisms are the major contributors to statin-induced diabetes[1,34,35]. Several molecular mechanisms have been argued in the literature:Statins can disturb insulin secretion affecting calcium channels in the β-cells; They downregulate GLUT4 (glucose transporter) resulting hyperglycemia; they decrease some downstream products, such as coenzyme Q10, farnesyl and geranylgeranyl pyrophosphates. Depletion of these important products disturbs intracellular signalling. Other mechanisms are inhibition of adipocyte differentiation, modulation of leptin and adiponectin. Genetic links and epigenetic regulations via differential expression of specific micro RNAs have also roles[1,14,32,36].

Pancreatic β-Cells and L-type Ca^{2+} channels

In the pancreatic β-cells, voltage gated Ca^{2+} (CaV; L-type) channels play an important role in insulin release. Dysregulation of these channels impair glucose homeostasis[7]. It is suggested that long-term cholesterol synthesis may disrupt the channel function together with insulin vesicle mobilization[37]. There is no clear mechanism proposed for this phenomena, however these effects may be due to conformational changes of the membrane and channel subunits[1,14,23]. On the other hand, statins have beneficial pleiotropic effects on the CV system by activating ATP-dependent potassium channels in the CV tissue. However, opening of these channels in the pancreatic β-cells causes inhibition of insulin secretion and this may lead to NODM[38].

Glucose transporters and caveolin

Statins can inhibit both calcium channel and glucose transporter 2 (GLUT2, predominant isoform in β-cells) protein expressions resulting disruption of insulin synthesis and release. GLUT2, K_{ATP} and CaV channel-mediated signalling chain is an important for insulin biosynthesis and release. On the other hand, HMG CoA reductase inhibition disrupts synthesis of isoprenoids, then the expression of GLUT4 is inhibited and causes impairment of glucose uptake. Caveolin-1 is an important protein which is localized in caveolae-rich regions where GLUT4 is translocated by insulin[1,12]. Khan *et al.*,[39] observed that simvastatin treatment in mice, caveolar vesicle docking is inhibited. Takaguri *et al.*,[40] also reported an alteration of GLUT4 translocation and reduced level after atorvastatin, but not pravastatin. Shortly, statins may disrupt translocation of GLUT4 in muscle, liver and adipose tissue, leading reduced glucose uptake, increased insulin resistance and hyperglycemia[14].

Insulin Signalling

Statin treatment may disturb insulin transduction cascade and can lead to insulin resistance[14]. Statins may alters phosphorylation steps and small G proteins[1]. RhoA and Rab4, small G proteins, have roles in the insulin signal cascade. Rab4 is a critical protein for glucose transport. It has been reported that GLUT4 expression was reduced because of decreased Rab4 function in adipocytes after atorvastatin[40].

Ubiquinone, adiponectin and leptin

Evidence indicate the role of ubiquinone (CoQ10), adiponectin and leptin on glucose metabolism. Statins may affect glucose homeostasis via CoQ10, adiponectin and leptin[12]. CoQ10 have a role in the regulation of mitochondrial function, which is important for pancreatic β-cells. Statins may induce myopathy by reducing CoQ10 production, however it is not well known yet whether there is a link between risk of insulin resistance or increased risk of NOMD.In adipocytes CoQ10 can reverse the reduction of GLUT4 induced by simvastatin[41]. Experimental data indicate that CoQ10 improves pancreatic β-cell function, insulin sensitivity and mitochondrial function[42]. We need more research about supplementation of CoQ10 to protect development of NODM during statin therapy

Reduced adiponectin levels may associate with obesity, insulin resistance and diabetes. Some results indicate that adiponectin can decrease insulin resistance[12,35]. Statin trials have been shown a decrease, increase, or no change in adiponectin levels[35]. Hydrophilic statins have generally been shown to increase adiponectin levels. Pitavastatin in some studies, improves insulin sensitivity and it has consistently been shown to increase adiponectin levels[12,35]. It is not clear whether lipophilic and hydrophilic statins have differential effect on adiponectin levels. Leptin, satiety factor, has been shown to be decreased by atorvastatin, rosuvastatin and simvastatin, but not by pravastatin or pitavastatin, in clinical studies[35,43]. Statins may increase food intake and weight gain in the long term. This may associate with decreases in leptin expression, but the results are still conflicting[43].

Inflammation

Inflammation can promote insulin resistance and/or diabetes[44]. Statins generally exert anti-inflammatory effects mainly by their pleiotropic effects. Statin use reduces C-reactive protein and may decrease the risk of myocardial infarction[12]. They also reduce many inflammatory events, such as changing cytokine profiles. They reduce tumor necrosis factor (TNF) and interleukin (IL)-6 (pro-inflammatory cytokines). But, conversly, they can increase IL-1β (pro-inflammatory cytokine), by reducing prenylation of proteins. According to the "inflammatory hypothesis of statins" they exert pro-inflammatory effects in dysmetabolic states by activating of some inflammasomes leading

IL-mediated insulin resistance.This concept requires more study[34].

Genetic link

HMG CoA reductase single nucleotide polymorphisms (SNPs) can lead a small increase in the risk of NODM[33,35,45]. A study (Mendelian) showed this association between genetic variation in the HMG CoA reduktaz gene (rs17238484 and rs12916 alleles) and inreased risk of NODM by statin treatment[12,33].

On the other hand, epigenetic changes can explain NODM risk such as, miRNA regulation, and DNA methylation (DNAm), particularly at genes for lipid or insulin regulation[46]. A recent epigenome-wide association study has investigated the association between statin use and changes in DNAm at sites in CpGs genome and found an evidence on DNAm partially mediating statins' effects[46].

Increased hepatic gluconeogenesis is an important mechanism for statin- induced NODM. However, the exact mechanism(s) is not clear. Aging is a strong risk factor for NODM and aging associated molecules may have roles on the development of NODM in statin use. It has been reported that aging related molecule Sirt6 may repress gluconeogenesis. In a recent study, simvastatin has been shown to induce miR-495 (a novel inhibitor of Sirt6) and down regulate Sirt6 expression in mice liver. Hence, this leads gluconeogenesis in the liver. Further, mRNA levels of Pck1, G6pc, and Ppargc1, as a gluconeogenesis genes, was found to increased in the liver of statin treated mice. Thus, it is suggested that Sirt6 activation may be a good strategy to prevent NODM[47].

DISCUSSION AND CONCLUSION

After the JUPITER study, potential mechanisms involving on statin-induced NODM has been searched intensively. It seems a multiple mechanisms are involved in this adverse effect. Potentiating insulin resistance (increased hepatic gluconeogenesis, inhibition of GLUT4 translocation) or decreased insulin release (β-cell dysfunction) have been proposed as major mechanisms[9,12,45]. There is also genetic link and intense research is going at the molecular level[48]. Statin type (potency, dose), patient characteristics (cardiovascular risk, age) and the pre-diabetic state are possible determining factors. Statins are associated with a modest increase in the risk (about one per thousand patient-years) and their benefits in preventing CVD outweigh the risk of NODM. It is important that before starting therapy the risk of NODM should be determined[10,13].

During therapy, patients should be monitored for glycaemic control. Lifestyle changes and controlled diet are important to reduce the risk. Moderate-intensive statin therapy is less diabetogenic than intensive therapy. If diabetes develops, it should be managed according to the guidelines[13,16,35]. Statins are recommended diabetic patients since they benefit from therapy regarding to CV risk[49]. In chronic dibetic patients, the effect of statins on glycaemic control is small and may be clinically not important. It is not recommended to stop the statin therapy in patients with NOD since statins have important effect in reducing CV risk[15,50]. On the other hand, statins may have fewer benefits in elderly people because of they have a short life expectancy and comorbidities.Thus, the benefits and disadvantages of statins should be evaluated carefully in elderly individuals[49].

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