Review Article

DIABETOGENIC EFFECT OF STATINS: MOLECULAR MECHANISMS

ABSTRACT

Statins, hydroxymethyl glutaryl coenzyme A reductase (HMG CoA) inhibitors,are potent hypolipidemic drugs. They are widely used in the primary and secondary prevention of cardiovascular diseasesand some of the most commonly prescribed medications worldwide. Statin therapy is associated with a modest increase in the risk of new-onset diabetes after long term therapy, and there has been great interest in the possible mechanisms for this adverse effect. Multiple molecular mechanisms have been proposed primarily related to increased insulin resistance and decreased insulin secretion. The risk for statin-related diabetes depends on many factors including age, pre-existing diabetic risk, type and potency of statin. But the consensus is that the benefits of statins in preventing cardiovascular disease events clearly outweigh the potential risk of diabetes.The aim of this review is to give underlying pathomechanisms and clinical relevance of diabetogenic effect of statins.

Key words: statins, diabetogenicity,adverse effect, mechanism, risk

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, and hypercholesterolemia is one of the major CVD risk factors[1]. Statins (HMGCoA) reductase inhibitors) were first approved by the US Food and Drug Administration (FDA) in 1987 and remain the first-choice drugs for their potent cholesterol-lowering effects.Since then statins have become the most prescribed drugs worldwide[2,3]. In addition to lowering LDL-C, statins have shown pleiotropic effects facilitating cardioprotective properties including improvement of endothelial dysfunction, antioxidant properties, inhibition of inflammation and stabilization of atherosclerotic plaques[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].As the prescription rates for statins have increased, more adverse effects have been identified, with the most common being increased liver enzymes and myopathy[1]. However, major statin trials indicate a definite increase in the development of new-onset diabetesmellitus (NODM) with statin therapy, especially in the presence of pre-existing diabetic risk factors, such as older age, obesity, woman, impaired glycemic control and insulin resistance, patients with lower baseline LDL(low density lipoprotein)-C levels, lower achieved LDL-C levels, and a large LDL-C level reduction[10,12].Data suggest a 10-22%higher risk of NODMwith statin use compared to nonusers. The risk increases with intensive treatment[13,14].While this effect has been thought to be a drug class effect, recent data suggest that pravastatin and pitavastatin could exhibit neutral effects on glycaemic parameters in patients with and without diabetes[13].

Type 2 diabetes mellitus (T2DM) is a strong, independent risk factor for CV outcomes[15]. As T2DM is accompanied by dyslipidemia, statins have a major role in preventing the long term complications in diabetes and are recommended for diabetics with normal LDL-C levels as well[16].The benefits of statins on CV risk reduction outweigh any harm related to their diabetogenic effect.

Currently, there are seven statin drugs available on the market: Pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin, fluvastatin and lovastatin. They are classified

according to their hydrophobicity into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (atorvastatin, fluvastatin, lovastatin, pitavastatin and simvastatin).

NODM risk was first demonstrated in the JUPITER trial (*Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluation Rosuvastatin)* in 2008,and then greater attention has been given to this issue[17,18]. Since that time the literature has largely supported this increased risk with other statins as well[19-23].Treatment with high doses resulted in a further increase by 10%, but there were no new cases of NODM among patients with no diabetes risk factors at baseline in JUPITER study[24].In March 2012, the FDA decided there was sufficient evidence to warrant a warning about increased diabetes risk being added to the packaging of all statins[25]. It appears though that the risk of diabetes is limited to people already at high risk for developing diabetes such as the elderly, women, obese, those with the metabolic syndrome, Asian ancestry, and patients with CVD and hypertension[26-28]. The trials did not indicate an increased risk of diabetes-related complications, such as nephropathy, neuropathy and retinopathy with statin therapy.

The effects of different statins on the risk of NODM are controversial. In the first two years of regular statin use, Dormuthh et al.[29] reported that higher potency statin use is associated with a moderate increase in the risk of NODMcompared with lower potency statins in patients treated for secondary prevention of CVD. 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[29-31].Although structural differences based on lipophilic or hydrophilic features have been proposed to be the possible mechanisms of stain-induced NODM[9] recentclinical studies have demonstrated no apparent difference in the diabetogenic effects between lipophilic and hydrophilic statins[32].Thuswe need more datato determine potential differences among individual statins. Accumulating evidence from several statin trials, population-based studies, clinical studies, and *in vitro* studies suggests that pravastatin is the least diabetogenic statin[33].In a new cohort study, compared with rosuvastatin, less diabetogenic effect of pitavastatin were observed among patients treated with moderate-intensity statin regimen[32].

Molecular mechanisms

Studies suggest that the effect of statins on glucose homeostasis reflect inhibition of HMGCoA reductase. *In vitro* and *in vivo*data indicate that statins reduce synthesis of mevalonate pathway products leading to impaired pancreatic β-cell function and decreased insulin sensitivity and insulin release, but the exact mechanism(s) of diabetogenesis are still unclear[13].It seems decreased insulin secretion is the majorcontributor to statin-induced diabetes[1,34,35]. Several molecular mechanisms have been proposed: Certain statins affect insulin secretion through direct, indirect or combined effects on calcium channels in pancreatic β-cells; Downregulation of GLUT4 results in hyperglycemia; Decreases important downstream products, such as coenzyme Q10, farnesyl pyrophosphate, geranylgeranyl pyrophosphate and their depletion leads to reduced intracellular signalling. Other possible mechanisms areinhibition of adipocyte differentiation, modulation of leptin and adiponectin. Genetic links and epigenetic regulations via differential expression of specific microRNAshave alsoimportant roles[1,14,32,36].

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

It is well known that opening of voltage gated Ca^{2+} (CaV; L-type) channels have an important role in insulin secretion in the pancreatic β-cells. Functional changes or levels of Ca^{2+}channels impair glucose homeostasis[7]. It is suggestedthat chronic inhibition of cholesterol biosynthesis may disrupt the functional activity of CaV channels and insulin secretory granule mobilization and membrane fusion[37].There is no clear mechanism proposed for this

phenomena however these effects may be due to conformational changes of the channel subunits[1,14,23].

On the other hand, statins exert their beneficial pleiotropic effects on the CV system by activating ATP-dependent potassium (K_{ATP})channels in the CVtissue. However, simultaneous activation of K_{ATP} channels in the pancreatic β-cells leads to inhibition of insulin release which may lead to diabetes[38].

Glucose transportersand caveolin

Statins can reduce mRNA and protein expression of GLUT2 (glucose transporter 2: predominant isoform in β-cells)and CaV channel, thereby inhibiting insulin synthesis and secretion. Intracellular glucose uptake via GLUT2 initiates phosphorylation by glucose kinase and subsequently K_{ATP} and CaV channel - mediated signalling cascades for the synthesis and secretion of insulin. Inhibition of HMG CoA reductase by statin can suppress synthesis of isoprenoids which in turn also inhibits the expression of GLUT4 (another rate-limiting protein for glucose transport), leading to impaired glucose uptake.In the late adipocyte differentiation stages, it was demonstrated a decrease in caveolin-1, an important plasma membrane protein present in caveolae-rich regions where GLUT4 is translocated upon stimulation by insulin [1,12]. Khan et al[39]reported an inhibition of caveolar vesicle docking in mice treated with simvastatin. Takaguri et al[40] also found that after atorvastatin, but not pravastatin treatment, total GLUT4 level and the translocation were altered. Decreased glucose uptake and increased insulin resistance in adipose tissue, muscle and liver which may be due to reduced translocation of GLUT4, and consequently leads to hyperglycemia[14].

Insulin Receptor Substrate and Insulin Signalling

Several disturbances in insulin signal transduction mediated by statin treatment have been described in different tissues leading to insulin resistance[14]. It is suggested that statins reduces insulin signal transduction via inhibition of necessary phosphorylation events and altering cellular distribution of small G proteins[1]. Insulin receptor substrate (IRS-1) is critical for insulin signalling and is phosphorylated in response to insulin binding to the insulin receptor (IR). Through the phosphatidylinositol 3-kinase (PI3K) pathway, Akt becomes phosphorylated and mediates glucose uptake by controlling GLUT4 translocation to the plasma membrane. Atorvastatin treatment decreased phosphorylation of IRS-1 and Akt in a dose-dependent manner. Lovastatin has been shown to inhibit the phosphorylation of the IR β-subunit and prevent the association of PI3K with the IRS-1/IR complex. Another study found that atorvastatintreatment downregulated IRS-1 and IR β-subunit levels during adipocyte differentiation. However, Takaguri et al[40]found no change in mRNA level, protein expression or phosphorylation of IR in adipocytes treated with atorvastatin or pravastatin. They observed changes in GLUT4 with atorvastatin, and concluded that inhibition of its translocation was not due to changes in IR, but rather the intracellular transduction of the signal. The proteins RhoA and Rab4 are small G proteins involved in the insulin signal transduction via modification of IRS-1 and Akt phosphorylation. Rab4 is crucial for glucose transport. In adipocytes, it is involved in the transport of GLUT4 to the plasma membrane in response to insulin signals. Takaguri etal[40] have reported that decreased GLUT4 membrane expression by atorvastatin is partially mediated by loss of Rab4 function.

Ubiquinone, adiponectin and leptin

Recent evidence also highlights the role of ubiquinone (CoQ10), adiponectin and leptin, in the modulation of glucose metabolism. Statins may impair glucose metabolism via affecting on CoQ10, adiponectin and leptin[12].CoQ10 plays an important role in the regulation of mitochondrial function, which is critical for β-cell function. Statin therapy has been shown to reduce the production of CoQ10, and potentially induce myopathy, but it is unclear whether this contributes to impaired insulin sensitivity and increase risk of diabetes. CoQ10 has been shown to ameliorate the reduction in GLUT4 transporter by simvastatin in adipocytes[41].

More research is needed to determine whether supplementation of CoQ10 can prevent the development of diabetes especially in patients with preexisting diabetic risk and receiving statin therapy. According to the some experimental data CoQ10 administration improves pancreatic β-cell function, increases insulin sensitivity and preserves the mitochondrial function in the cells[42].

A decrease in adiponectin level might also link statin therapy to insulin resistance and diabetes.However, the role of adiponectin has not been clearly established[10,12]. Adiponectin is secreted by adipocytes, and low adiponectin levels are associated with insulin resistance and obesity.Evidence suggests that adiponectin may protect against the development of diabetes by improving insulin sensitivity[12,35]. Proposed molecular mechanisms of the effect of adiponectin on insulin sensitivity include inhibition of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver, stimulation of glucose uptake and fatty acid oxidation in the skeletal muscle[10]. However, clinical studies have been inconclusive, with increases, decreases, and no change in adiponectin levels by statin therapy[35]. It is unclear whether lipophilic and hydrophilic statins have differential effect on adiponectin metabolism. In contrast to lipophilic statins, hydrophilic statins (pravastatin, rosuvastatin and pitavastatin) are generally more consistent to increase adiponectin levels and insulin resistance.Pitavastatin has consistently been shown to increase adiponectin levels and, in some studies, it improves insulin sensitivity[12,35].

Leptin, an important satiety factor in appetite regulation is also secreted by adipocytes and has been shown to be suppressed by atorvastatin, rosuvastatin, and simvastatin, but not by pravastatin or pitavastatin, in humans[35,43]. Statin use is associated with increased calorie intake and weight gain. Decreases in leptin expression by statins may contribute, at least in part, to increases in food intake in the long term statin users. But the role of statins in regulation of leptin is still conflicting[43].

Inflammation

Inflammation can promote insulin resistance and /or diabetes[44]. Statins are generally anti-inflammatory, but HMGCoA reductase inhibition and targeted decrease in protein prenylation predominantly result in skewing immune responses toward anti-inflammatory characteristics, via pleiotropic effect. Statin use reduces in C-reactive protein which has been associated with a reduction of myocardial infarction risk[12].In addition to CRP, statins have been shown to reduce many inflammatory processes, including cell adhesion/migration and skewing cytokine profiles. They reduce pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6.But, the findings have shown that statins increase the pro-inflammatory cytokine, IL-1β, via decreased protein prenylation in immune cells. IL-1β can be regulated by the NLRP3 inflammasome containing caspase-1[34]. It is hypothesized (“inflammatory hypothesis of statins”) that, under dysmetabolic conditions, statins might have pro-inflammatory effects via induction of certain inflammasomes. On certain conditions, statins may activate inflammasome NLRP3 from macrophages or adipocytes in the presence of endotoxins, leading to IL-mediated insulin resistance.However, under physiological states, a moderate decrease in insulin sensitivity can be compensated by enhanced insulin secretion by pancreatic β-cells. This concept requires more study[34].

Geneticlink

Genetic studies suggest that the increased risk of NODM may be partially explained by gene variants in the target genes for LDL-C lowering drugs.There is evidence that HMG CoA reductase single nucleotide polymorphisms (SNPs) is associated with a small but discernible increase in the risk of diabetes, raised blood glucose and insulin, and higher body weight[33,35,45,].This observation was validated in the randomized statin trials, and one particular allele was associated with a significant increase in the risk of new diabetes. A recent randomization study (Mendelian study)reported that the inhibition of HMG CoA reductase

activity with statin, particularly due to genetic variation in the HMGCR gene (rs17238484 and rs12916 alleles), was associated with an increased risk of NODM[12,33],and this may at least partly explain their diabetogenic effect[33-35].

On the other hand, statins are associated with epigenetic changes, including histone acetylation,

miRNA regulation, and DNA methylation (DNAm), particularly at genes related to lipid and insulin metabolism[46].Arecent epigenome - wide association study has investigated the association between statinuse and changes in DNAm at sites inthe genome called CpGs and found an evidence on DNAm partially mediating statins' effects. This could be one potential mechanism linking statin therapy and NODM[46].

Increased hepatic gluconeogenesis has been suggested as one of the primary mechanism for statin- induced glucose intolerance. However, the precise mechanism is not well known yet. Since aging is the primary risk factor in NODM, aging related molecules may be involved in glucose dysregulation caused by statin. Agingrelated molecule Sirt6 has been reported to repress hepatic gluconeogenesis.In a recent study simvastatininduced miR-495 (a novel inhibitor of Sirt6) and down regulatedSirt6 expression, which leads to enhancement of FoxO1-mediated hepatic gluconeogenesis in mice liver. mRNA levels of gluconeogenesis genes such as Pck1, G6pc, and Ppargc1a were increased in the statin-treated liver. Thus, Shi et al.[47] have suggested that Sirt6 activation may offer a promising strategy for preventing NODM.

DISCUSSION and CONCLUSION

Since the publication of the JUPITER trial, attention has been focused on the adverse glycemic effects of statin therapy.Whilemolecular basis remains unclearit appears that the potential diabetogenic effects of statins may involve multiple mechanisms.*In vitro* and population studies have revealed possible explanations. Potentiating insulin resistance (increased hepatic gluconeogenesis, inhibition of GLUT4 translocation and of adipocyte differentiation) or decreased insulin secretion (the direct or indirect effects on β - cell function)have been proposed as major mechanisms[9,12,45]. There is also evidence of an association between alleles influencing lipid metabolism and the risk of diabetes.Intense research is currently going on to elucidate the mechanisms of statin- induced NODM at the molecular level[48].

Intensive statin therapy is more diabetogenic than moderate-intensity therapy. The possible determining factors are the drug characteristics (potency, dose), patient characteristics (kidney function, age, cardiovascular risk) and the pre-diabetic state.Although statin therapy is associated with a modest increase in the risk (about one per thousand patient-years), the consensus is that the benefits of statins in preventing CVD events clearly outweigh the potential risk of diabetes.Before initiation of statin therapy the risk of NODM should be assessed in patients[10,13]. During therapy, high risk of patients should be monitored for changes in blood glucose. In addition, diet and lifestyle interventions should be emphasized to reduce the risk of NODM.Diabetes is diagnosed only 2-4 months earlier in statin-treated patients, and if diabetesdevelops, it should be managed according to the guidelines[13,16,35].On the other hand, diabetic patients are one of the groups that benefits most from statin therapy with regards to CV risk, and statins are recommended in patients with diabetes and hypercholesterolemia, to prevent CV events[49].Indiabetes of long duration, the effect of statins on glycaemic control is small and unlikely to be clinically important.Thus, diabetic individuals should receive statin treatment to reduce CVD.Considering the important effect in diminishing CV risk in all patients, including those with diabetes, it is not recommended to stop the statin therapy in patients with pre-existing or newly diagnosed diabetes. Patients who develop NODM while using statins do not exhibit increased microvascular disease[15,50].On the other hand,since elderly people have a shorter life expectancy and more comorbidities than younger people,

statins may have fewer benefits in this population. Thus, the benefits and disadvantages ofstatins should be evaluated carefully in elderly individuals[49].

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