

Possible Diabetogenic Effects of Statins Therapy and its Clinical Implications

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ABSTRACT

Statins, hydroxyl-methyl-glutaryl-coenzyme-A reductive inhibitors, are efficacious and safe drugs used for the management of hyperlipidemia and preventing primary and secondary cardiovascular disorders. This reduction is directly proportional to the reduction of LDL-cholesterol. However, different population-based and Meta-analyses studies showed an incidence of new-onset diabetes mellitus (NODM). Older age, females, obesity, Asian descent, the potency and intensity of statin therapy, existing metabolic disorders, altered blood glucose levels, and increased weight are highly prone to diabetes. Although, the definitive cause of new-onset diabetes mellitus is not ruled out, plenty of mechanisms have been suggested including inhibiting HMG-CoA reductase, decreasing expression of GLUTs, modifying lipoprotein particle size, decreasing adiponectin and ubiquinone levels. These mechanisms result in either increasing insulin resistance or decreasing insulin secretion. In addition, under dysmetabolic situations, statins may have pro-inflammatory effects through the induction of certain inflammasomes. According to existing evidence, prescribing this class of drugs should not be restricted in patients with high cardiovascular risk due to their risk is lower than their benefits. However, close monitoring of commonly available lab tests is recommended.

Key words: Adverse effects; Diabetes, Diabetogenicity, Statins

INTRODUCTION

Statins are potent, selective, competitive, and reversible inhibitors of HMG CoA reductase. This enzyme is responsible for the conversion of HMG CoA to mevalonate during cholesterol metabolism. Statins compete with HMG-CoA (an endogenous substrate) on the active site of the enzyme. The higher affinity statins bind to the active site of the enzyme and bring conformational change, thereby preventing HMG-CoA binding [1]. This ultimately leads to blockage of de novo cholesterol synthesis [2]. The inhibition of this enzyme by statins reduce LDL-C formation in the blood. Statins also upregulate LDL receptors in the liver and peripheral tissues, increasing the removal of LDL particles from the blood. The activity of these receptors is a vital determining factor for plasma LDL concentrations [1,2] Generally, statins have a direct effect on lipid metabolism and an indirect effect on intracellular cascades [3]. Their indirect effect is mostly related to their effect on prenylated proteins. Inhibiting mevalonate cascade by statins causes reductions in GGPP, FPP, dolichol (cofactor in N-linked glycosylation), and coenzyme Q10 [4].

Currently, fungal derived (Lovastatin, pravastatin, and simvastatin) and synthetic (atorvastatin, fluvastatin, pitavastatin, and

rosuvastatin) statins are available for clinical use [3]. Cerivastatin was known for its fatal rhabdomyolysis and it was withdrawn from the market in 200 [5]. All these statins have three parts: HMG-CoA (enzyme-substrate) analog, a hydrophobic ring structure and side groups on the ring [3]. Statin therapy is effective in lowering LDL-C levels by 20-50%, as well as lowering triglyceride levels by 10-20% and causing a possible rise in serum HDLC) levels by 5-10% [4]. Management with these drugs has transformed primary and secondary prevention of CVD [6].

Statins have pleiotropic effects other than their lipid reduction properties, such as stabilizing atherosclerotic plaques, improving vascular endothelial function, reducing vascular inflammation & platelet aggregability, immunomodulatory, antithrombotic, angiogenesis promotion, anti-oxidant effects and increase in bone formation [4]. They may reduce the risk of ischemic heart disease, ischemic stroke, left ventricular hypertrophy, arrhythmias, myocardial infarction, the need for arterial revascularization, possibly atrial fibrillation, Alzheimer's disease, type 2 diabetes, slow the progression of chronic nephropathies, rheumatoid arthritis, and multiple sclerosis [6]. These pleiotropic activities of statins are supposed to be responsible for the clinical benefits of statin therapy [4]. As the usage of these drugs has increased, many adverse events

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have been identified from lifelong use, with prominent effects on liver and muscle [7].

Additional clinical trial evidence indicates that the use of these drugs is associated with enhanced risk of NODM and in February 2012 the US FDA has added warning information concerning the “effect of statins on incident diabetes and increases in HbA1C and/or fasting plasma glucose” to statin safety labels in patients who already have diabetes [8]. The present review aims to explore the evidence from Meta-analyses and clinical trial studies concerning the possible diabetogenic effects of statins, probable mechanisms of this association, and how this evidence might change the clinical use of these drugs.

METHODS

Statin therapy in patients with diagnosed DM

Diabetic clients are often associated with an increased cholesterol level. The death of these clients is majorly caused by atherosclerotic CVDs. Therefore, statins are often prescribed for diabetic patients [9]. The risk of CVD and T2DM enhanced with hyperlipidemia, indicating that lipid-lowering agents for CVD might have protecting effects on pancreatic islets, which in turn prevent the onset of T2DM. Different clinical trials on patients with T2DM showed a significant decrease in CVDs after statin treatment [7,9].

Statin and new-onset diabetes mellitus

Even though these drugs are effective, safe, and well-tolerated, current data from different clinical trials, post-hoc studies, Meta-analyses of RCTs, short-duration studies, observational studies, and Mendelian randomization methods have confirmed that they might increase the risk of diabetes, especially in those predisposed patients [10-13].

The association between statin administration and incident diabetes was first reported from the West of Scotland Coronary Prevention Study (WOSCOP), which showed a 30% decrease in the risk of incident diabetes in those patients taking 40 mg of pravastatin. This report was in line with basic science data, which states a protecting activity of statins for the development of diabetes [10]. Contradicting to this evidence, statins diabetogenicity effect

was reported from JUPITER trial study (An Intervention trial evaluating rosuvastatin). According to this study, there was a 25% increased risk of diabetes in those clients taking Rosuvastatin 20 mg [12]. Like the JUPITER trial, the Pravastatin in Elderly Individuals at Risk of Vascular Disease study (PROSPER) showed a 32 % increased risk of diabetes in those taking pravastatin [14]. The findings of these two trials (JUPITER and PROSPER) were in agreement with reports from other RCTs that showed an increased risk of diabetes with statin usage [10,13] On the other hand, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, reported no effect of a 40 mg pravastatin on NOD as compared with control groups [15].

Generally, a review of the current scientific data indicates a consistent association of statin usage and an enhanced risk of T2DM development. Plenty of other clinical trials on Atorvastatin, Rosuvastatin, and Simvastatin reported increased fasting blood sugar levels and increased hemoglobin A1c [11].

Risk factors predisposing to statin-induced NODM

Post hoc analyses of different trials indicate the risk of DM with statin treatment increases in those patients with multiple metabolic syndromes [11]. This risk is especially high in individuals with prediabetes (plasma glucose >100 mg/dl), metabolic syndrome, family history of T2DM, obesity (BMI >30 kg/m²), sedentary lifestyle, atherogenic and diabetogenic dietary practices, older patients, women, Asian ethnicity, diabetogenic medications coadministration, hyperlipidemia, hypertension patients and the intensity of the statin [16,17]. An increased adherence to statin treatment in diabetic patients reduce the risk of macro vascular complications but at the same time, the risk of NODM increased progressively with this increased adherence [18,19].

Pathophysiologic mechanisms of statin-induced NODM

The clear molecular mechanism of statins induction to NODM is complex. However, several pathophysiologic mechanisms have been postulated which ultimately decrease either insulin secretion or sensitivity. As shown in Figure 1, different mechanisms can serve as a base for the association of statin treatment and risk of NODM [20]. These drugs could raise blood sugar levels by increasing

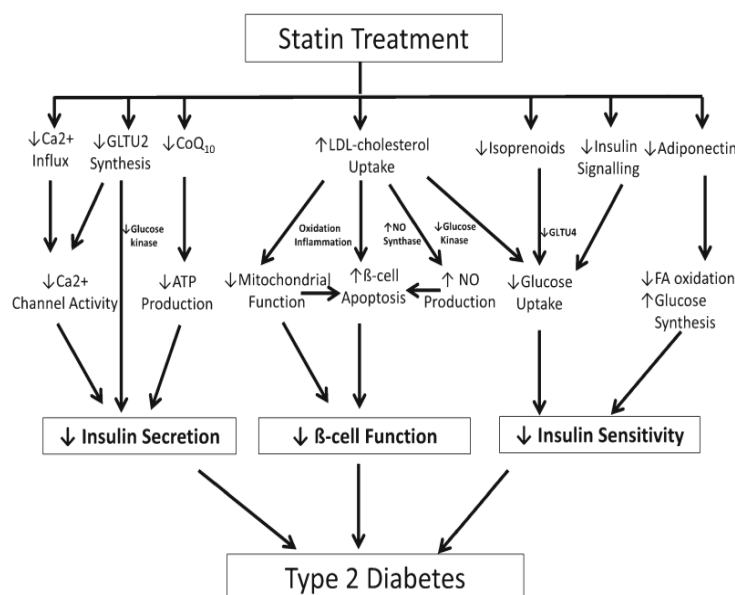


Figure 1: Potential mechanisms of action in the development of diabetes.

insulin resistance of skeletal muscle, adipose tissue, and the liver. They impair pancreatic beta-cell secretory activity, insulin signaling pathways, myocyte/adipocyte insulin sensitivity, mitochondrial & skeletal muscle function, and exercise tolerance [16,20].

Different studies indicated that the diabetogenicity of statins is mediated through different pathophysiologic mechanisms [10]. Therefore, there are many ways that statins can cause insulin resistance, pre-diabetes, and diabetes.

HMG-coenzyme A reductase inhibition

The glucose-raising effects of an on-target activity of statins were investigated with the Mendelian randomization principle. From the result, statins HMG-CoA reductase activity, particularly genetic variation in the HMGCR gene was linked with an enhanced risk of T2DM. (21) This suggests that an on-target effect of statins is associated with the risk of diabetes. Therefore, the risk of DM is causally associated with the intensity of HMGCR and statins potency. Determination of an on/off-target effect of statins on DM risk help to understand the drug or drug class effect of these drugs on glucose metabolism [21,22].

Upregulation of LDL receptor

Reducing the activity of HMGCR causes LDL receptors upregulation, which leads to increased removal of LDL cholesterol to replace intracellular concentration. The fate of plasma-derived cholesterol may be different from *de novo* synthesized cholesterol. Endogenous cholesterol is essential for the normal activity of pancreatic β 2 cells [23]. The concentration of this cholesterol can change the secretory activity of β 2 cells by modulating calcium channel function as well as insulin granule mobilization and membrane fusion. The influx of cholesterol through the LDL receptor impairs β -cell activity, proliferation, and survival, while its efflux through ATP-binding cassette transporters restores the biological activity and survival [24]. Increased concentration of plasma-derived cholesterol can inhibit glucose kinase, which interferes with normal glucose uptake [23,24].

In familial hypercholesterolemia patients, where there is a gene mutation of LDL receptor, apolipoprotein B and Proproteinconvertase-subtilisin/Kexin type 9, statins do not escalate the risk of DM [25,26]. These patients were also reported with a low incidence of diabetes as compared to their control relatives or hyperlipidemic patients, even during an intensive treatment with statins. Therefore, the mutation of the LDL receptor in these patients might prevent the onset of diabetes and the diabetogenicity of statins [27].

B-cell inflammation, oxidation, and apoptosis

Oxidation of plasma-derived cholesterol might lead to activation of the immune response which causes inflammation and oxidation process that ultimately affect the functional and structural integrity of β -cells, thereby interfering with glucose metabolism [1]. Current evidence also suggests that statins could activate NLRP3 (inflammatory protein) from macrophages/adipocytes in the presence of endotoxins like lipopolysaccharide (LPS), causing IL-1 β mediated insulin resistance [12]. During dysmetabolic state gut microbiomes might be altered, providing the LPS protein that activates the inflammasomes which mediate the paradoxical inflammatory effects of statins [1]. This statins induction of inflammation and mitochondrial dysfunction in skeletal muscle,

beta cells, and adipocytes were associated with the pathogenesis of insulin resistance and DM. For example, in β -cells mitochondria are essential to couple glucose metabolism with insulin exocytosis and their dysfunction might cause β -cell apoptosis and death [1].

Three mechanisms have been proposed for the effect of statins on nitric oxide (NO) synthesis and bioavailability: up regulation of endothelial nitric oxide synthase (eNOS) activity, enhanced endothelial nitric oxide synthase expression, and stabilization of endothelial nitric oxide synthase mRNA. (1) Overproduction of NO due to cytokine induction was reported to induce β -cells apoptosis via the activation of calpain, a calcium-dependent protease. Overall, inflammation, oxidation, and apoptosis – triggered by the influx of plasma cholesterol due to impairment *de-novo* cholesterol synthesis by statins might cause the pathogenesis of DM during long term usage of these drugs [1,8,12].

Inhibition of coenzyme Q10 biosynthesis

Coenzyme Q is a lipid-soluble molecule with a side chain of 10 isoprenoid units. (1) Its production is modulated by HMGCR enzyme in the mevalonate pathway. It can occur in reduced (ubiquinol) or oxidized (ubiquinone) form; transition between them allows it to function as an electron carrier in the mitochondrial respiratory chain [4].

This molecule is available in all cellular membranes, blood, and lipoproteins, but more concentrated in the heart, kidney, liver, and muscles due to the high energy requirement of these [28]. Different mechanisms were suggested to associate statins induced depletion of this molecule and DM. Biologically, it functions as an energy transporter in mitochondrial and extra-mitochondrial membranes. It accepts electrons from and transfers them to the cytochrome complex which, in turn, drives ATP synthesis [28,29]. So its deficiencies can affect the electron transport chain there blocking ATP production and causing reduction of insulin secretion. This molecule was also reported to play an essential role in GLUT4 production [29]. Thus, its inhibition might cause a reduction in the expression of this transporter in adipocytes, which in turn leads a reduction in glucose uptake. This molecule has been also reported with antioxidant and free-radical scavenger activity, which protects plasma membranes and lipoproteins from oxidative damage [30]. The deficiency of this molecule was suggested to decrease the beta cell activity, thereby impairing glucose metabolism [19,31].

A reduction of this molecule in muscle tissue can affect mitochondrial function, which enhances the risk of statin-induction of myopathy. Its depletion also causes myocyte inflammation and fiber damage. This might be a possible pathophysiologic mechanism of statins to induce myopathy and insulin resistance in skeletal muscle [29]. The decline of this molecule with aging was associated with oxidative stress and mitochondrial dysfunction in skeletal muscle, which accelerates statins induction of peripheral insulin resistance. Administration of CoQ10 can help to replace its plasma concentration in clients taking statins [29]. In addition, evidence has confirmed that CoQ10 supplementation improves beta-cell function & insulin sensitivity and preserves the mitochondrial function in the islets [28].

Clear mechanisms of antidiabetic or insulin-sensitizing effects of this molecule were not confirmed. However, upregulation of insulin and adiponectin receptor, stimulation of insulin signaling pathways, and elevation of soluble receptor for advanced glycation end products (sRAGE) have been suggested as possible mechanisms [31]. Generally, different pieces of evidence showed the essential

role of this molecule in the modulation of mitochondrial activity beta-cells. However, there is no clinical data that show the direct linkage of CoQ10 deficiency and the onset of DM [31].

Inhibition of adiponectin

Different adipocytokines (adipocyte-derived molecules) have been discovered that can affect glucose metabolism and lead to insulin resistance and DM [31]. These adipocytokines include leptin, adiponectin, resistin, visfatin, retinol-binding protein-4, interleukin-6, and tumor necrosis factor- α (TNF- α) [32]. Adiponectin and leptin were known for their mediating activity for the diabetogenicity of statins [31].

Adiponectin (plasma protein) augments and mimics metabolic and vascular actions of insulin and exerts key beneficial effects on carbohydrate metabolism [32]. In humans, plasma levels of these proteins are negatively related to insulin resistance [31]. Different data showed that adiponectin may protect DM development by improving insulin sensitivity.

Plenty of mechanisms of adiponectin action on insulin sensitivity have been suggested, which includes: suppressing gluconeogenesis, stimulating fatty acid oxidation in the liver, stimulating glucose uptake & fatty acid oxidation in skeletal muscle [32]. It can also stimulate the expression of insulin gene & insulin secretion in beta cells by the induction of extracellular signal-regulated kinase and Akt phosphorylation in the insulin signaling pathway. Moreover, adiponectin was reported to enhance mitochondrial biogenesis and fatty acid oxidation in skeletal muscle by activating mitogen-activated protein kinase (MAPK) and PPAR- γ coactivator 1 α (PGC-1 α) [32]. In addition, the anti-inflammatory effect of this molecule can protect beta-cell function and viability, which improves tissue (especially the liver and muscle) insulin sensitivity [19,31].

Low levels of adiponectin are strongly associated with genetic factors which might contribute to increased DM risk. Single nucleotide polymorphisms in the gene of adiponectin were reported to be associated with hypo adiponectinemia and increased DM. Since these low levels of adiponectin correlate with insulin resistance and obesity, statins' inhibitory effect on this molecule is a possible mechanism for NODM (Table 1) [33].

Inhibition of leptin

In the previous study, leptin is reported to have a key role in the regulation of beta-cell mass.(32)Leptin resistance and/or reduced leptin levels (comparative leptin deficit) are supposed to play a significant role in insulin secretion, insulin resistance, and diabetes mellitus by several mechanisms, such as a negative effect on insulin secretion and β -cell proliferation. According to the previous finding, reduction in leptin level is linked with rosuvastatin,

simvastatin, and atorvastatin regimen and undesirably influences the proliferation of beta-cells and insulin secretion, consequently causing the development of DM [31,33]. Through leptin-receptors, leptin passes in the hypothalamic appetite/satiety center, in which it signals mitochondria to yield a host of hormones and substances including melanocortins. The produced melanocortins are supposed to stimulate muscle cells to burn glucose at a faster rate [34].

Inhibition of glucose transporters

In several clinical trials, statins revealed to prejudice the glucose uptake by different cells (skeletal myocytes, adipocytes) that have a key role in the regulation of glucose metabolism through triggering the glucose transporter proteins (cholesterol-dependent conformational changes in the GLUT).[35] Cholesterol is essential for the strengthening of membrane lipids; it rigidifies the fluid plasma membrane to raise its thickness and mechanical properties and decreases passive permeability. Accordingly, the statin-stimulated cholesterol diminution disrupts the construction of membrane-embedded proteins, including glucose transporter proteins [36].

In normal circumstances, glucose enters into the pancreatic adipocytes, skeletal muscle cells, and β -cells through insulin-responsive transmembrane glucose transporter (GLUT)-2 and -4 and it is the most vital signal for insulin secretion [35]. Glucose transporter, particularly GLUT-4 is accountable for glucose entrance to skeletal muscle cells and adipocytes cells. Through impeding glucose transporter (GLUT) gene expression, statins impair glucose metabolism by preventing its uptake in pancreatic islet β -cells, skeletal muscle cells, and adipose tissue cells. Both in vitro and in vivo studies revealed that statins can reduce the expression of the insulin-responsive glucose transporter 4 in adipocytes through inhibition of the production of isoprenoids resulting in diminished the post-translational modification of small G proteins and glucose uptake, that is crucial in insulin-containing granule exocytosis. Isoprenoids (FPP and GGPP) are known to improve glucose uptake via the upregulation of glucose transporter type 4 in adipocytes [37]. Glucose transporter type 4 is disseminated into the cell compartment in the basal state and displaces to the cell membrane in reply to insulin signaling [38]. Glucose transporter type 4 fusion with the adipocyte's plasma membranes is regulated by an intracellular signaling pathway. This involves the IRS-1 and several kinases, including the phosphoinositide-3 and the Akt. Glucose transporter type 4 expression in the skeletal muscle diminishes with age, this justifies the more diabetogenic effect of statin therapy in elderly. Furthermore, treatment with statin has shown a significant reduction in energy and intensifications of fatigue, these are predominantly protuberant in females. The

Table 1: Statin's effects on various adipocytes affecting molecules.

Molecule	Physiological effects of the molecule	Effect of statins
Adiponectin	Decrease liver gluconeogenesis Increase insulin secretion	Reduced by atorvastatin, simvastatin Neutral or increase by atorvastatin, pravastatin, simvastatin, fluvastatin
Visfatin	Mimics the effects of insulin Provide hypoglycemic effects	Reduced by rosuvastatin, atorvastatin Neutral effect by simvastatin
Resistin	Increase blood sugar level Increase glycogen breakdown Increase glucose production	No/little effect by statins (mostly atorvastatin studies)
Leptin	Effects on insulin signaling and hepatic gluconeogenesis	Reduced by rosuvastatin, simvastatin, and atorvastatin Neutral effect by pravastatin, atorvastatin

associated adverse effects in the muscles by statin treatment could impair exercise capacity, decrease in muscle function and mass and perpetuate sarcopenia, sarcopenia responsible for the occurrence of insulin resistance, leading to pre-DM and DM [39].

On the other hand, glucose is transported into the β -cells by GLUT2. Inside β -cells, enzyme glucokinase play a key role is in the phosphorylation of glucose to glucose-6-phosphate. After sequential metabolic pathways, adenosine triphosphate (ATP) is synthesized. Adenosine triphosphate is an indispensable regulator of insulin secretion by acting on the subsequent opening of calcium channels, membrane depolarization, and the K ATP channel. Secondary to membrane depolarization resulting in calcium influx via L-type calcium channels triggering exocytosis of insulin-containing granules [35]. This process may be inhibited by statins since statins are capable of inhibiting the gene expression of voltage-dependent calcium channel and GLUT2, thus constraining secretion and synthesis of insulin [40].

Inhibition of L-type calcium channel

Cytosolic Ca^{2+} may play a key role in the signaling for glucose-mediated insulin secretion by pancreatic beta cells. When intracellular calcium within pancreatic β cells increases, insulin secretion is initiated [39]. L-type Ca^{2+} channels might play a key role not only in the glucose-mediated but also in L-arginine- and KCl-stimulated insulin secretion. Cytosolic Ca^{2+} concentration appears to be dependent on the intracellular cholesterol content. Inhibiting endogenous cholesterol biosynthesis by statins may block the L-type-mediated Ca^{2+} influx, thus reducing its cytosolic concentration. [41]. This effect may be predominantly apparent for the lipophilic rather than the hydrophilic statins. Certainly, the lipophilic statins have a high affinity for the cell membrane than hydrophilic statins, hence they can easily enter into the intracellular space. Thus, these statins are supposed to inhibit endogenous metabolic pathways linked to glucose-induced insulin secretion (Ca^{2+} -dependent insulin responses to glucose and endogenous cholesterol synthesis) [39]. Animal model has shown that simvastatin inhibits calcium channels, leading to inhibition of calcium signaling of the pancreatic beta cells. Similarly, in vivo studies revealed that Pravastatin can inhibit calcium channels, nevertheless, Pravastatin produces this effect at higher doses than clinically used doses [41].

Inhibition of insulin signaling

In the previous studies, statins revealed a significant effect in the stimulation of small GTPases, which have a role in the expression of glucose transporter type 4 in the plasma membrane by intracellular insulin signal transduction [39]. When insulin or insulin-like growth factor (IGF) is bound to the insulin receptor (IR), the Insulin receptor substrate (IRS-1) becomes phosphorylated and which is important for insulin signaling. Thru the phosphatidylinositol 3-kinase (PI3K) path, serine-threonine kinase AKT is subsequently phosphorylated/activated and mediates glucose uptake through regulating the glucose transporter type 4 translocation to the plasma membrane by facilitating the transport of storage vesicles comprising GLUT4 to the cell membrane [33]. Rab4 and RhoA are small G proteins responsible for insulin signal transduction through alteration of the phosphorylation of Akt and IRS-1. Rab4 is crucial for insulin-stimulated glucose transport. Small GTP-binding proteins play a key role in the signaling for insulin secretion by pancreatic beta cells as a response to both glucose and

Ca^{2+} . These proteins require isoprenylation for their association with the cell membranes. For example, Rab proteins are altered in an animal model and involve isoprenylation to link with vesicular membranes. This procedure is intermediated thru mevalonate products, such as FPP and GGPP [39].

Statins block the signaling for insulin secretion elicited by both glucose and KCl via inhibiting mevalonate synthesis. It is proposed that statin therapy accountable to DM through dropping insulin signal transduction by changing the cellular spreading of small G proteins and the embarrassment of essential phosphorylation proceedings. Statins may also disrupt several other early events of insulin signaling. These comprise mitogen-activated protein kinase and tyrosine phosphorylation of the insulin receptor b subunit [33,39].

Statins revealed a reduction in the expression and phosphorylation of IR membrane, leading to insulin resistance. Inside the cell, Glucose transporter type 4 and insulin signaling may be transformed thru variations in Akt, Rab4, IR- β , RhoA, IRS-1, and Ras, all of these could be repressed by statin treatment. Different statins including atorvastatin, cerivastatin, and lovastatin have been shown to affect different factors such as IRB, Rab4, Akt, IRS1, P13K, RhoA, Ras, caveolin-1, and IGF [39].

Tyrosine phosphorylated IRS-1 contains binding sites for crucial signaling proteins, such as the p110 and p85 subunits of phosphatidylinositol 3-kinase, thru stimulation of the PKC and Akt cascades, which plays a significant role in insulin secretion and release [33]. Activation of AKT stimulates glycogen production thru the embarrassment of protein synthesis, cell survival, and glycogen synthase kinase 3 β (GSK3 β) through inhibition of forkhead box protein O1 (FOXO1; a transcription factor), Bcl-2-associated death promoter (BAD; a proapoptotic factor) and GSK3 β . P, phosphate group; PI, phosphatidylinositol. The association of the p85 subunit of phosphoinositide-3 kinase with insulin receptor substrate-1 (IRS)-1 and the initiation of the mitogen-activated protein kinase may be inhibited by statins [33,42].

Modification of lipoproteins particle size

Statins could also cause NODM through their modifying effects on lipoprotein particle size. Statins therapy have shown a reduction in the size of HDL-C, LDL-C, and the lipoprotein insulin resistance (LPIR) score, however increment in the size of very-low-density lipoprotein cholesterol (VLDL-C) particles, these leading to an increase in the occurrence of NODM. Though, small VLDL-C particle sizes, large HDL-C particle sizes, and large LDL-C particle sizes have a reverse outcome on NODM [43].

Clinical considerations

The potential risk of DM related to the initiation of statins therapy highlights the critical importance of balancing scientific evidence with patient preferences and clinical judgment [44]. Detecting patients who would benefit more from the use of less diabetogenic compounds or smaller doses can help to improve the management and decrease the number of individual developing diabetes mellitus throughout hypolipidemic treatment with statins. There is no doubt that the use of statins in patients with high cardiovascular risk is fully authenticated [7]. However, it is still ambiguous where exactly lies the point beyond which statins' beneficial and protective cardiovascular actions begin to outweigh their small, nevertheless apparent, diabetogenic risk. In people with very high values of

LDL-cholesterol and/or higher cardiovascular risk necessitating more aggressive therapeutic modalities, use of more potent statins therapy, nevertheless of worse metabolic profile, can't be deprived of [44].

The increased risk of developing diabetes mellitus incontrovertibly has to be considered when introducing simvastatin or rosuvastatin, but can't be an excluding factor for such therapy. Alternatively, statin therapy is one of the most effective approaches for CVD prevention. Furthermore, it is critical to reminisce, that statins can't be considered for all diabetes mellitus new cases detected during the hypolipidemic management. However, consistent investigation of a few commonly available laboratory tests such as oral glucose tolerance test, fasting glucose, and glycated hemoglobin along with a regular follow up of diabetes mellitus risk factors should be recommended in patients chronically using statins [7,44].

At large, special consideration such as optimization of the hypocholesterolemic treatment by selecting appropriate doses and statins, and control of baseline glycemic markers should be given to high-risk patients with DM.(7) Furthermore, it is crucial to consider different factors that affect the diabetogenic response of statins therapy, identifying the more vulnerable people. Therefore, factors such as statin of choice, patient's carbohydrate metabolism, patient characteristics, and dyslipidemia treatment should be considered in the choice of a statin for the management of dyslipidemia in patients with prediabetes or DM. In addition, it is important to consider other factors that may not be directly linked to hypocholesterolemic when evaluating the use of a statin in patients with carbohydrate metabolism disorders.

Overall, there are some steps which may help to offer extreme protection from cardiovascular disease at the same time evading new-onset diabetes such as start with low doses, prescribe only when indicated, choice of individual statin, lifestyle modifications, patient information about the risk, screening of patients, monitoring and vitamin D supplementation since vitamin D shortage has been associated with insulin resistance and supplementation of vitamin D has revealed to recover insulin sensitivity. Patients who are taking statins should be screened for vitamin D deficiency and managed accordingly [8].

Even though there is contradictory suggestion rotating around different statins triggering DM, the large cardiovascular benefit compensates for the possible risk of new-onset

DM. Thus, the commendations on treatment with statin continue unpretentious by current studies. Since the risk of new-onset DM is still being characterized, and it seems to be significantly outweighed by the considerable decreases in CVD mortality, treatment with statins remain the drug of choice for prevention of cardiovascular disease [20,33]. Though, it has been revealed that the risk of new-onset DM differs reliant on types of statins, doses, and individualized treatment based on the patient's risk profile [33]. During the development of NODM, switching to a more advantageous statin (pitavastatin or atorvastatin), reducing the dose of statin, and alternate-day administration of statin is generally recommended. Though, if a modification in statin regimen and dose reduction causes a reduction in cholesterol control, the preceding statin dose should be continued and antidiabetic medications should be added to the regimen [20].

According to data from the Cholesterol Treatment Trialists' Collaboration, dropping LDL-cholesterol by 1 mmol/l result in 20–25% reductions in relative risk reduction (RRR)/vital cardiovascular events including coronary revascularization, stroke, and myocardial infarction [44]. Furthermore, statin-related diabetes mellitus risk appears to be confined in people with diabetes risk factors. Contrasting the deep-rooted benefits of LDL-C dropping on atherosclerosis, the long-term macrovascular effects of statin-related diabetes mellitus is uncertain (Table 2) [44].

DISCUSSIONS AND CONCLUSION

The risk of diabetes mellitus with statin therapy is dose and type-dependent and appears to be consistent with their HMG-CoA reductase inhibition capacity. Statins have variable grades of lipophilicity: simvastatin, atorvastatin, pitavastatin, lovastatin, and fluvastatin are lipophilic, while rosuvastatin and pravastatin are hydrophilic. Lipophilic statins passively diffuse through the hepatocellular membrane, whereas hydrophilic agents require carrier-mediated uptake. Subsequently, lipophilic statins are capable of diffusing across extrahepatic tissues, hence reducing their hepato-selectivity. Based on the current evidence, the use of different statins should not be withdrawn from people who are at high cardiovascular risk, even if they are prone to NODM, because their benefits outweigh their risks. However, consistent investigation of a few commonly available laboratory tests such as oral glucose tolerance test, fasting glucose, and glycated hemoglobin along with a regular follow up of diabetes mellitus risk factors

Table 2: Selection of statin in patients with alterations in glucose metabolism.

Selection based on	Age of the patient
	Estimated diabetes mellitus risk
	Estimated cardiovascular risk
	Regular monitoring of glucose levels
	Fasting plasma glucose levels
	Albuminuria levels
	Polypharmacy, where applicable
	Renal function
	Patient's HbA1c levels
	Selection of a statin that doesn't worsen carbohydrate metabolism
General diabetogenic profile	Atorvastatin is well-thought-out the most diabetogenic
	Not all have diabetogenic effects
	Differs among the different statins
Selection of drug	Pitavastatin doesn't have a diabetogenic effect
	In the opinion of the experts, pitavastatin is the best drug of choice in pre-diabetic or DM

should be recommended in patients chronically using statins. If NODM develops, statin treatment should not be stopped, but a switch to the administration of a more favorable statin, administration of statin on alternate days, or reduction of the dose should be considered, or antidiabetic therapy added. HMG-coenzyme A reductase inhibition, upregulation of LDL receptor, β -cell inflammation, oxidation, and apoptosis, inhibition of coenzyme Q10 biosynthesis, inhibition of adiponectin, inhibition of leptin, inhibition of glucose transporters, inhibition of L-type calcium channel, inhibition of insulin signaling, and modification of lipoprotein particle size are the mechanisms of statin-induced NODM.

ACVD, atherosclerotic cardiovascular disease; CoQ10, Coenzyme Q 10; eNOS, endothelial nitric oxide synthase; FH, familial hypercholesterolemia; GLUTs, glucose transporters; HDLC, high-density lipoprotein cholesterol; HMG-CoA, hydroxyl-methyl-glutaryl-coenzyme-A; IRS-1, insulin receptor substrate 1; IGF, insulin-like growth factor; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LPS, lipopolysaccharide; VLDLC, very low-density lipoprotein cholesterol; NODM, new-onset diabetes mellitus; and T2DM, type 2 diabetes mellitus.

COMPETING INTERESTS

The authors declared that they do not have any conflict of interest.

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AUTHORS' CONTRIBUTION

AgumasAlemu Alehegn and Mohammedbrhan Abdelwuhab contributed to the conception, study design, execution, acquisition of data, and interpretation. Zemene Demelash Kifle and Agumas Alemu Alehegn took part in drafting, revising, or critically reviewing the article. All authors read and approved the final manuscript.

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