Can Statin be a Novel Pharmacophore for Antidiabetic Activity ?

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Abstract: Currently, statins are in lime light due to their pleiotropic effects. One of their pleiotropic effects is on glucose metabolism. Various clinical and preclinical studies were designed to evaluate statins' effect on glucose metabolism. This review describes preclinical and clinical evidences of statins' action on glucose metabolism.

Key Words: Statin, diabetes, insulin resistance, glucose metabolism, solubility.

INTRODUCTION

Diabetes is one of the leading causes of adverse cardiovascular events (CVE). Relation between diabetes and CVE is well established [1]. This increased risk is because of alteration of homeostatic balance like altered insulin receptor mechanism, hyperglycemia [2], disturbed lipid levels etc. [1,3,4]. It is well known that diabetic dyslipidemia is the key factor for high adverse CVE [5]. Several anti-dyslipidemic therapies have decreased morbidity and mortality in diabetic patients [6-9]. Amongst anti-dyslipidemic therapies, statins are highly promising agents. Initially they were used as lipid lowering drugs only but now due to pleiotropic effects their use are proposed in several clinical situations [10]. This review article deals with the evidence based effects of statins on glucose metabolism.

MECHANISM OF ACTION AND STRUCTURE ACTIVITY RELATIONSHIP

Statins belong to the group of lipid lowering drugs, which act by inhibiting 3-hydroxy 3-metyl glutaryl CoA (HMG Co-A) reductase enzyme. HMG CO-A is involved in rate limiting step of cholesterol synthesis pathway. This enzyme is responsible for conversion of HMG Co-A to mevalonate. Statins are structural analogues of HMG Co-A with better affinity and thus competitively inhibits HMG Co-A reductase. By inhibiting this enzyme, statins lower the synthesis of cholesterol in liver (Fig. (**1**)). This leads to increment of LDL receptors on the hepatocyte, which ultimately causes decrease in plasma LDL level. Apart from lipid lowering activity they also decrease triglyceride & apolipoprotein A level and slightly increase HDL cholesterol level [11].

Chemically statins have two parts i.e. ring with hydrophobic substituents and a side chain (dihydroxyheptanoic acid moiety) (Fig. (**2**)). The ring structure is analogue of coenzyme A moety of endogenous substance (HMG CoA). The ring is responsible for adjustment of statin molecule on enzyme binding site and also for solubility profile of individual statins. Different ring structures which are present in currently available statins are partially reduced napthylene (lovastatin, simvastatin and pravastatin), Pyrrole (atorvastatin), Indole (fluvastatin), pyrimidine (rosuvastatin), quinoline (pitavastatin) etc [12]. Moreover, statins contain at least 2 hydrophobic substituents on these rings. Ring along with hydrophobic substitutions is responsible for high affinity of the statins compare to endogenous substrate because of higher number of van der waals interaction [13].

Side chain (dihydroxyheptanoic acid) is structurally similar to 3-hydroxy 3-metyl glutaryl. It binds to active site of the enzyme and is must for statins' inhibitory activity. This side chain contains either free carboxylate group or lactone ring. Statins containing lactone ring are pro-drugs and get activated when this ring is hydrolysed and produce free carboxylate group.

Based on their water solubility statins have different pharmacokinetic profiles and tissue specificity (Table **1**). Hydrophilic statins have shorter half life and more selectivity toward liver (site of action) compare to lipophilic statins [14]. Lipophilic statins by passive diffusion can penetrate in to various extra-hepatic tissues.

STATINS IN DIABETES

Statins have shown promising outcomes in clinical trials involving diabetes associated adverse CVE [6,15]. However, controversial data are also available. It has been proven that diabetes associated dyslipidemia shows characteristic lipid profiles**.** High LDL can increase cardiovascular complications in diabetes patients, but it is not a characteristic of diabetes associated dyslipidemia [16]. The occurrence of high LDL in diabetic patients is same as in normal population. In diabetes there is accumulation of chylomicron, apolipoprotein B and VLDL. HDL and LDL are enriched by triglyceride which leads to decrease in HDL as well as increase in small, dense LDL. In addition to this impaired suppression of hepatic VLDL synthesis after meals is also observed [17]. Small dense LDL particles are responsible for high rate of adverse events in diabetes [18].

Though statins do not have direct effect on small dense LDL particles, they are very useful in diabetic population and also in cardiac patients without diabetes. This shows greater protection than it is to be thought by only lipid balancing activity. This may be due to pleiotropic effects, which

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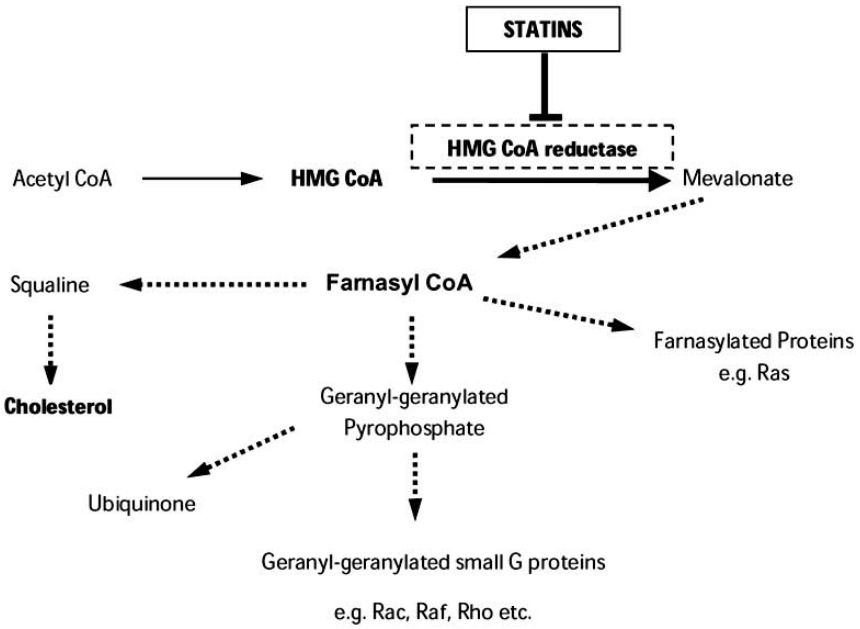

Fig. (1). Effect of statins on synthesis of cholesterol and isoprenylated proteins.

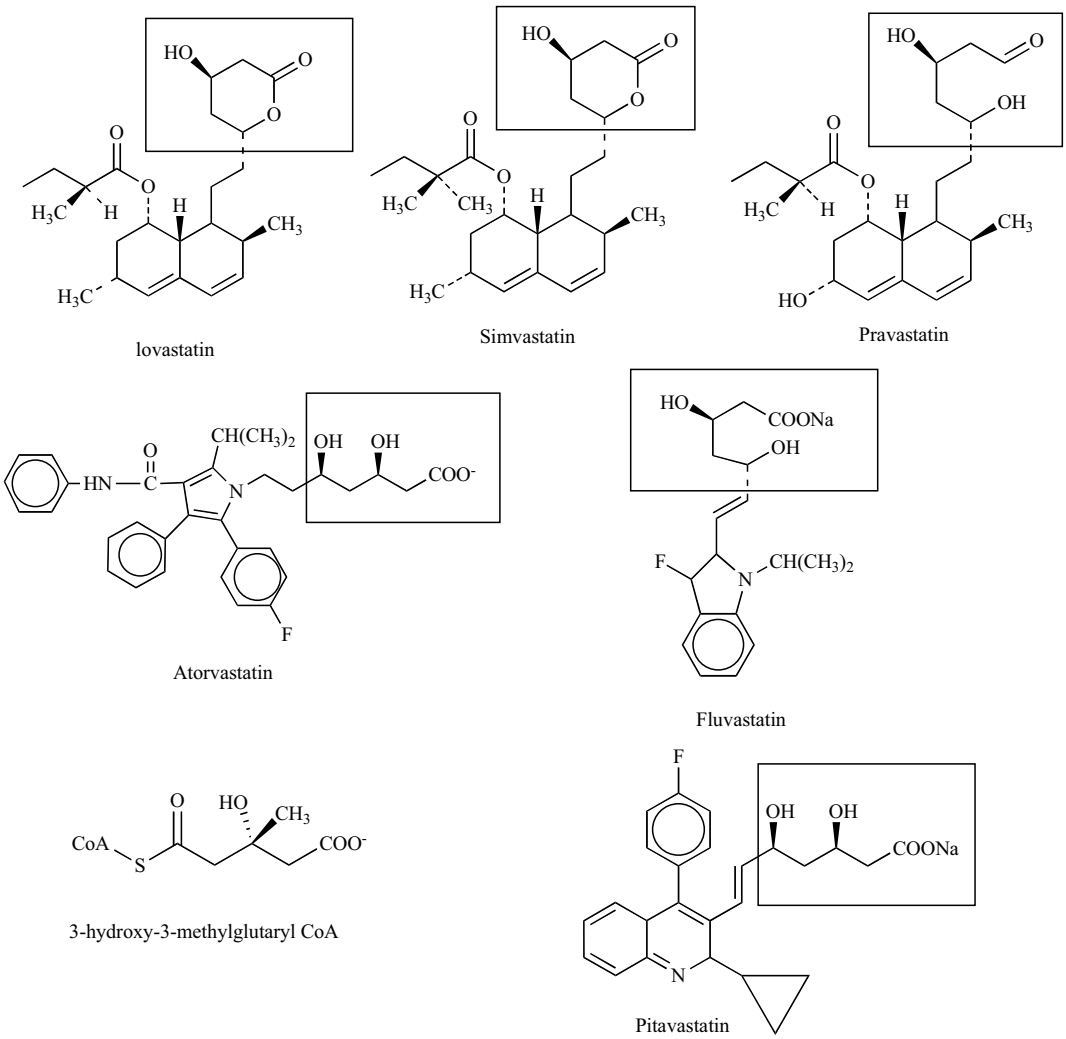

Fig. (2). Chemical structures of HMG CoA and statins. Box indicates side chain involved in competitive binding with HMG CoA for HMG CoA reductase.

Table 1. Pharmacokinetic Comparison of Statins [14,45]

Statins	LDL Cholesterol Reduction (%) and Dose (mg)	Solubility	Bioavaibility (%)	CYP450 Isoenzyme	Active Metabolite	Elimination Half Life (Hour)	Renal /Fecal Excretion (%)
Atorvastatin	38%–54% (10–80)	Lipophilic	12	3A4	YES	14	Urine <2 Feces 98
Lovastatin	17%–33% (20–80)	Lipophilic	5	3A4	YES	3	Urine 10 Feces 83
Fluvastatin	25%–44% (0.2–0.8)	Lipophilic	24	2C9	NO	1.2	Urine 5 Feces 90
Simvastatin	52%–63% (10–40)	Lipophilic	5	3A4	YES	2	Urine 10 Feces 60
Pravastatin	29%–48% (20–80)	Hydro-philic	18	NO	NO	1.8	Urine 20 Feces 70
Rosuvastatin	19%–40% (10–40)	Hydro-philic	20	Limited	Minor	19	Urine 13 Feces
Pitavastatin	20%-42% (1-10)	Lipophilic	80	Limited	Minor	11	NA

are independent from cholesterol lowering effects [19]. One of the major reasons for pleiotropic effects of statins is that the cholesterol synthesis pathway is also involved in production of some very important biomolecules [19]. As shown in Fig. (**1**), cholesterol synthesis pathway is involved in synthesis of isoprenylated proteins, fernasylated proteins, geranylgeranylated proteins etc which are very important regulators in various dynamic activities of the cell. Summary of various pleiotropic effects of statins are given in Table **2**.

In this review we have focused on *statins' effects on glucose metabolism* especially in diabetes.

EFFECTS OF STATIN ON GLUCOSE METABOLISM

Clinical Studies

In sub-analysis of West of Scotland Coronary Prevention Study [20,21], pravastatin has shown significant reduction (30 percent) in development of type 2 diabetes mellitus in treated group. It was proposed that this action of pravastatin may be due to its anti-dyslipidemic and anti-inflammatory activity. This result showed that statins might have protective effects on insulin resistant patients who are at a risk of type 2 diabetes. Study involving group of insulin resistant patients showed improved fasting & prostprandial glucose levels, insulin sensitivity and decreased Homeostasis Model Assessment (HOMA) in pravastatin treated groups [22]. Authors proposed that these effects of pravastatin may be due to its anti-inflammatory activity. It is proven that pravastatin can decrease the level of TNF-α, which is one of the factors responsible for insulin resistance. In two different studies on type 2 diabetic patient and hypercholesterolemic patients without diabetes, pravastatin showed beneficial effects as compare to atorvastatin for improvement of insulin sensitivity [23,24]. In these studies it is also reported that atorvastatin may adversely affect beta cell function. Study on aged dyslipidemic type 2 diabetic patients showed that simvastatin and atorvastatin have beneficial effects on insulin sensitivity and atorvastatin have higher efficacy as compared to simvastatin [25]. Other clinical studies on atorvastatin have shown that it may detoriate glycemic control in type 2 diabetic patients [26,27]. While some studies on atorvastatin [28], simvastatin (40mg/day) [29] and Lovastatin (80mg/day) [30] showed no significant change in insulin sensitivity in the treated group compare to placebo. All of these clinical studies have used parameters like HOMA, fasting and postprandial glucose, glycosylated hemoglobin, oral glucose tolerance test, insulin level etc. as a measure of insulin resistance. These studies were only aimed to determine whether statins do have any effects on glycemic control in diabetic patients. So, clear mechanisms for such effect are not attained from study. Most of the clinical studies proposed that it may be due to statins effect on triglyceride levels and partly due to anti-inflammatory activity.

Pre-Clinical Studies

Based on the observation obtained from the clinical studies various pre-clinical studies involving *in vitro* and *in vivo* techniques were performed to determine mechanism of action of statins for their effect on glucose metabolism in diabetes. One of the *in vitro* studies by Yada *et al.* showed that lipophillic statin (Simvastatin) can inhibit glucose induced cytosolic calcium signaling in pancreatic beta cells while hydrophilic statin (pravastatin) failed to show any effect [31]. Glucose induced calcium signaling is responsible for glucose dependent insulin secretion from pancreatic beta cells. It was concluded that lipophilic statins might adversely affect glucose metabolism. Apart from this study various *in vivo* studies were also carried out using different animal models for diabetes. Some studies failed to show any effect

Table 2. Pleiotropic Effects of Statin [10,19]

1. Anti-inflammatory activity
Decreases TNF α, NFκB, IL 1, IL 6 and CRP
2. **Prevent oxidative stress**
Inhibits NADPH oxidase and conversion of LDL to oxidized LDL
Increases glutathione and ubiquinone in LDL particles thioredoxin
3. Endothelial function and vascular smooth muscle proliferation
Induces eNOS and iNOS
Alters release and action of Ang II and ET 1,
Inhibits VSMC proliferation and migration
4. Atherosclerosis and thrombosis
Decreases PAI-1 and modulates fibrinogen levels
Decreases CD36 and MMP-9,
Increases collagen content of plaque
5. Renoprotective effects
Decreases TGF-β and Inflammatory markers in kidney cells
6. Bone remodeling
Decreases activity of osteoclast
Decreases bone resorption and activates bone formation
7. Glucose metabolism
Improves insulin signaling pathway in insulin resistance,
Protects β cell from oxidative stress, increases insulin release

TNF α: Tumor necrosis factor α, NFκB: Nuclear Factor κ B, IL interleukin, CRP: C reactive protein, LDL: low density lipoprotein, eNOS: endothelial nitric oxide synthase, iNOS: inducible nitric oxide synthase, AngII: Angiotensin II, ET1: endothelin 1, VSMC: Vascular Smooth Muscle Cell, MMP: matrix metallo proteinase, PAI: Plasminogen Activator Inhibitor, CD36: Cluster of Differentiation 36, TGFβ: Transforming growth factor beta.

of statins on glucose metabolism while other studies have shown significant effect of statin therapy on glucose metabolism. Based on these studies various mechanisms are proposed for statins action on insulin resistance. Studies on STZ induced diabetic rats showed no effect of statins on glucose levels and OGTT but atorvastatin lowers glucose level at various intervals without alteration of insulin secretion [32]. In Goto-Kakazaki rats, Satoh *et al.* have reported that pravastatin, simvastatin and atorvastatin do not produce any significant change in insulin resistance [33]. Pravastatin shows gender specific change in islet blood flow (IBF) and total pancreatic blood flow (PBF) [34]. In male goto-kakazaki rats pravastatin improves both IBF and PBF and thus increases serum insulin levels while in female rats it only improves PBF. Huang *et al.* reported that Nitric oxide synthase (NOs) inducing activity of statins might be responsible for such enhanced blood flow [35]. Atorvastatin is reported to have multiple effects on adipocytes. *In vitro* studies have shown that it inhibits insulin dependent glucose uptake in white fully differentiated adipocytes but not in pre-matured undifferentiated adipocytes [36]. In high fat diet fed animal models of type 2 diabetic animals, statins improve insulin resistance in liver and muscle cells [37]. Further, lovastatin has

Table 3. Summarizing Effects of Statins on Insulin Signaling and Secretion

Improvement of insulin sensitivity
↓ Tg
↓ TNF-α and NFκB
↑ PPARγ activation and synthesis
↑ PI3K/ Akt pathway mediated effects of insulin
↓ Membrane cholesterol which in term increases insulin effect
↓ IRS 1 and PTP 1b
Increases Insulin secretion
↑ NOS
↓ DPP IV

also shown improvement of insulin resistance in liver of HFD fed rats [38], through its action on insulin signaling-pathways. It enhances PI3K/Akt pathway which in term increases glucose uptake. Atorvastatin can upregulated PPAR γ levels and thus may improve insulin sensitivity [39]. It also inhibits IRS 1 serine phosphorylation and NFκB which are responsible for attenuation of insulin signaling. Lovastatin also inhibits a key negative regulator, Protein phosphatase 1B (PTP-1B) of insulin singaling pathway [38]. Rosuvastatin, a comparative hydrophilic statin has improved insulin resistance in liver of fructose fed insulin resistant rats [37,40], however in clinical studies it failed to show such kind of effects. Apart from these effects, statins also possess enzyme inhibitory activity. Recently it is proven that statins can inhibit dipeptidyl peptidase IV (DPP-IV) [41]. DPP-IV is serine protease, responsible for degradation of Glucagon like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP). GLP-1 and GIP plays important role in glucose homeostasis as both are responsible for 70% of insulin secretion after meal. Thus by inhibiting DPP-IV statins can increase insulin secretion. Atorvastatin shows high level of DPP-IV inhibiting activity compare to rosuvastatin and simvastatin. In addition to these, atorvastatin is reported to have inhibitory effect on liver glucose 6 phosphatase enzyme, which is responsible for gluconeogenesis [40]. Recently Howarth *et al.* proved that *in vitro* treatment with atorvastatin exhibits insulin sensitizing activity in 3T3 L1 adipocytes by lowering membrane cholesterol content [42].

Kanda *et al.* have reported that long term treatment with Rho-kinase inhibitors improves glucose and lipid metabolism in Zucker obese rats [43]. They have proven that this is due to inhibition of serine phosphorylation in IRS 1 and thus improves insulin sensitivity in skeletal muscle. Thus drugs like statins acting through inhibition of isoprenylation and Rho-kinase may be consider as new therapeutic target for anti-diabetic action.

From above studies it is clear that lipophilic statins show somewhat consistency in their effect on glucose metabolism compare to hydrophilic statins.

DOES SOLUBILITY OF STATINS PLAY ROLE?

Based on chemical structure, statins can be classified according to their solubility profile. Soubility of statins plays

major role in important biochemical processes like absorption, distribution, metabolism and excretion. Atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin are relatively lipophilic compounds while Pravastatin and rosuvastatin are relatively hydrophilic. Hydrophilic statins show more hepatoselectivity (site of action) compare to lipophilic statins [14]. Thus lipophilic statins may have more potent effects on extrahepatic sites compare to pravastatin and rosuvastatin. As mentioned earlier, in various clinical and pre-clinical studies pravastatin have shown beneficial effects on glucose homeostasis. Rosuvastatin failed to show any effect in clinical study, but in pre-clinical studies it shows improvement in hepatic insulin resistance. Lipophilic statins especially atorvastatin showed variable effects in type 2 diabetes. In some studies atorvastatin adversely effects glucose control, while in some it is proven to be beneficial.

In preclinical studies all hydrophilic statins improved liver insulin resistance [37], while in clinical studies only pravastatin showed effect on glucose metabolism. This may be due to their hepatoselectivity and localized effect. In clinical studies, parameters for liver insulin resistance were not carried out which may be one of the reason for failure to get results.

DRUG-DRUG INTERACTION AND METABOLISM OF STATINS

Apart from distribution solubility also plays major role in metabolism and excretion of drugs. Diabetic patients are usually prescribed various drugs along with anti-diabetic drugs, which may be responsible for drug-drug interaction. Lipophilic statins like Atorvastatin, simvastatin, lovastatin are extensively metabolized by CYP 3A4 while fluvastatin is extensively metabolized by CYP 2C9 and thus there are high chances of drug-drug interaction [44]. Amongst statins Pravastatin does not metabolized by CYP 450 [14,45]. Thus, the only hydrophilic statin which shows improvement in glucose tolerance in clinical studies is Pravastatin. Apart from pharmaco-kinetic interaction there are chances that other commonly prescribed drugs in diabetic patient may have pharmacodynamic interaction with statins at molecular level. Although there is no strong evidence about effects of drug metabolism and drug drug interaction on glucose metabolism, these factors should be considered for future drug development.

CONCLUSION

Statins are very important class of drugs for the treatment of dyslipidemia. It is widely prescribed in patients having risk of adverse cardiovascular events, especially diabetic patients. Pleiotropic effects of statins on glucose metabolism and insulin signaling are very important for such patients Table **3**.

Diabetes is a very complex metabolic disorder. As our knowledge about molecular mechanism increased, we have designed drugs which can act very selectively to a single pathway or more correctly to a single molecular target. But this may not be fruitful *in diabetes as series of pathological events are present simultaneously. We need drugs like statins which can act on several pathological events simultaneously*. This will require intensive clinical investigations to identify properties of statins which are more potent in relation with insulin signaling and/or glucose metabolism e.g. balance between lipophilicity and hydrophilicity, selectivity to extra hepatic sites, metabolic characteristics, drug drug interactions etc. Thus, statins have potential to provide potent lead for novel antidiabetic molecule, acting on multiple pathophysiological pathway in diabetes.

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