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Mini Review

Effect of Statins Therapy in Diabetogenesis

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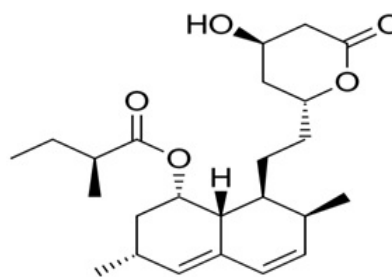
ABSTRACT

Statins are widely used in the management or inhibition of several processes that lead to the development of cardiovascular diseases. Increased statin therapy has been related to the induction of type II diabetes (DM), a state which predisposes to cardiovascular disease (CVD). Statins are well-known to possess anti-inflammatory properties and the ability to disrupt de novo biosynthesis of cholesterol and lipid homeostasis has been implicated in the induction of inflammatory responses within pancreatic β-cells. Inhibition of β-hydroxy β-methyl glutaryl-CoA (HMG-CoA) results an increased level of low-density lipoproteins (LDL) receptors. Increased LDL receptor numbers will replenish exhausted intracellular supplies, resulting in higher levels of intracellular cholesterol. Therefore, stimulating immunological response and inflammatory reactions, disrupt the functional integrity of the β-cell *via* oxidation of the plasma-derived low-density lipoprotein. Despite the pleiotropic effects of statins on the pancreatic β-cell, they have also been reported to affect a number of other cell types associated with the development of diabetes. Inhibition of the biosynthesis of isoprenoid by statins has been associated with the down-stream regulation of glucose transporter (GLUT 4) in adipose tissues, which facilitates the uptake of glucose. This effect resulted in increasing resistance to insulin in the liver, muscle, and adipose tissue. Adiponectin, a plasma protein released by adipocytes, alters fatty acids and carbohydrate metabolism both in the muscle cells and liver. This process indirectly influences resistance to insulin by the attendant decrease in hepatic gluconeogenesis and to upregulate muscular β-oxidation and glucose uptake.

INTRODUCTION

Among the most commonly prescribed drugs worldwide, are cholesterol-lowering agents statins - used to manage cardiovascular and other related heart diseases.[1] Even though statins have been proven to significantly reduce the risk of cardiovascular disease (CVD) and its associated mortality,[2] statins therapy may lead to an increased risk of type II diabetes (Figure 1).[3]

Statins function by controlling the metabolic pathway at the level of β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase in producing cholesterol. HMG-CoA reductase is the rate-controlling enzyme in the mevalonate pathway, which is the sole contributor to the production of cholesterol. As a result, it is the target for pharmacokinetics to utilize inhibitors to reduce the production of cholesterols while increasing the expression of low-density lipoproteins (LDL) receptors.[4]

Figure 1. Structural Analogue of Statins (Simvastatin)

The binding of statins to the mammalian HMG-CoA reductase at lower concentrations causes a displacement effect of the substrate HMG-CoA, which then binds at a concentration of micromolar.[5] Interactions between HMG-CoA reductase and stat-

ins inhibit the conversion of HMG-CoA to L-mevalonate, leading to the inhibition of down stream cholesterol biosynthesis and numerous metabolites such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP1) (Figure 2).
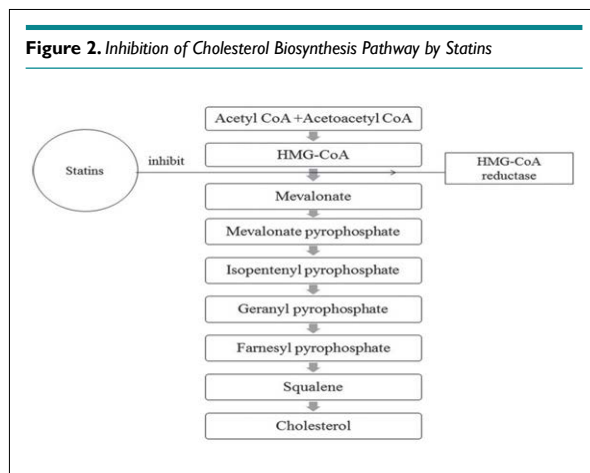
Figure 2. *Inhibition of Cholesterol Biosynthesis Pathway by Statins*
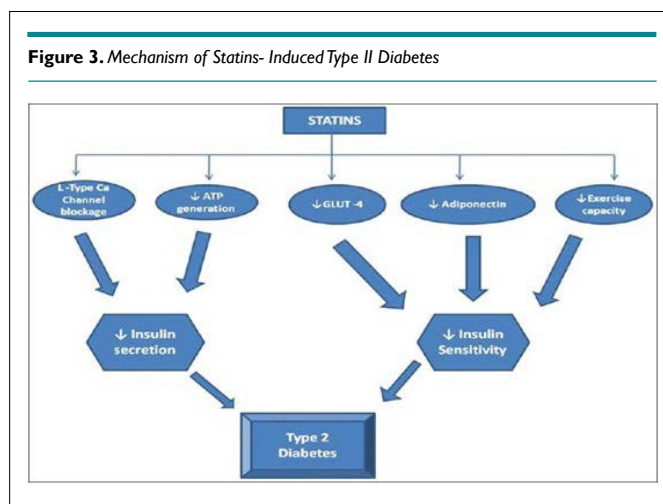
PATHOPHYSIOLOGY AND ETIOLOGY OF TYPE II DIABETES

Type II diabetes is triggered by a mix of genetic factors associated with compromised insulin secretion, resistance, and environmental factors including; obesity, stress, overeating, lack of exercise, as well as aging. It has also been reported that Japanese individuals may have many diabetes-sensitive genes including thrifty genes. The number of diabetic patients is rapidly increasing, reflecting the changes in lifestyle.[6]

STATINS AND TYPE II DIABETES

Though it is well-documented that statins considerably decrease the risk of developing CVD. Nonetheless, statin chemotherapy could lead to an increased risk of type II diabetes.[2] Current theories of type II diabetes mellitus include a defect in insulin-mediated glucose uptake in muscle, a dysfunction of the pancreatic β-cells, a disruption of secretory function of adipocytes, and impaired insulin action in the liver.[3]

PRECISE MECHANISMS OF DIABETOGENICITY

Statins-induced diabetes remainsun certain; meanwhile, there have been several proposed mechanisms, most of which fall within two distinctive domains (Figure 3). The major mechanism associated with statin-induced diabetes is β-cell dysfunction, which included altered insulin secretion and sensitivity, changes in ion channel conductance, and oxidative stress and inflammation.

Statins may also induce diabetes *via* the dysregulation of insulin secretion endogenously. The major signal for the release of insulin from the pancreatic β-cell is glucose. Glucose is taken up into the pancreatic β-cells *via* glucose transporter 2 (GLUT2), where it is phosphorylated to glucose-6-phosphate (G-6-P) by either the glucokinase or hexokinase IV enzyme. Subsequently, the

glycolytic pathway is activated, leading to increased production of adenosine triphosphate (ATP), which later closes the ATP-gated potassium ion channels resulting in membrane depolarization.

Figure 3. *Mechanism of Statins- Induced Type II Diabetes*

Depolarized membrane promotes the influx of calcium ion through L-type calcium channels, induce exocytosis of insulin granules. Statins, on the other hand, inhibit voltage-gated calcium channels in the β-cells of the pancreas resulting in decreased insulin secretion and insulin retaining granules exocytosis.[7] Rosuvastatin has been shown to have an inhibitory effect on glucose-induced insulin secretion through the inhibition of HMG-CoA reductase, rather than the calcium channels of the pancreas, as this action can be reversed by mevalonic acid.

It has been shown that specific statin drug, rosuvastatin influence the secretion of insulin *via* the same pathway it affects the cholesterol levels. Also, the levels of coenzyme Q10 can be reduced by statins. CoQ10 is a constituent of the electron transport chain involved in the generation of ATP.[8] Delayed production of ATP can be a result from reduced levels of CoQ10 and subsequently, diminished release of insulin.[9] Pancreatic β-cell mitochondrial dysfunction, skeletal muscle cells, and adipocytes have been implicated in the pathogenesis of diabetes.[10-12] Aside from reduced secretion of insulin from pancreatic β-cells, noteworthy evidence proposed that insulin sensitivity can be altered with statin-use and precipitate widespread insulin resistance. Therefore, it was assumed that diabeto genesis might be related to the consequence of statins on insulin sensitivity in the liver and muscle.[13] Inhibition of isoprenoid biosynthesis by statins has been implicated in the downregulation of glucose transporter (GLUT4), which mediates glucose uptake in the adipocytes.[14] Down regulation of GLUT4 results in enhanced resistance to insulin in adipocytes, muscle, and liver.

The metabolism of carbohydrates and fatty acids in liver and muscle influences insulin resistance by reducing hepatic gluconeogenesis and upregulating glucose uptake and beta-oxidation in the muscle, which is affected by the adiponectin released from the adipocytes. Therefore, insulin resistance has been shown to have a pathophysiological effection type II diabetes development.

Although, statins have been shown to have a beneficial effect in reducing the susceptibility to cardiovascular events, however, its glycemic implication on patients should be examined frequently by evaluating the glycemic index irrespective of the patient developing diabetes or not. Further studies are important to determine whether or not the dose and duration of statins use could affect glycemic control.

STATINS TOXICITY

Statin is not synthesized in the animal or human body. Specific statins such as mevastatin, lovastatin, and pravastatin are natural statins drug of fungal origin,and simvastatin is a semi-synthetic drug derived from lovastatin. Meanwhile, fully synthetic satins are atorvastatin, cerivastatin, fluvastatin, pitavastatin, and rosuvastatin.[15,16] The general safety of statins is widely accepted, but there have been reports of adverse effects resulting in altered renal, hepatic, and musculature function.[17]

The most common adverse effects of statins are on the skeletal muscle, which ranges from a mild myopathy such as cramp, fatigability, and exercise intolerance to myotoxicity. In rare cases, severe rhabdomyolysis may develop.[18] Rhabdomyolysis is a complex health condition characterized by swift dissolution of damaged muscle with increment in the release of toxic intracellular muscle components. Simvastatin also induces apoptosis in cardiac myocytes,[19] human skeletal muscle cells,[20] T-cells, B-cells, and myeloma tumor cells.[21] Other possible toxicological effects of statin therapy include-hemorrhagic stroke, depression, and lower testosterone, decreased renal function, tendon rupture, elevated liver function tests, interstitial lung disease, among others.[22]

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the women's health initiative. *Arch Intern Med.* 2012; 172(2): 144-152. doi: 10.1001/archinternmed.2011.625

2. SHARP Collaborative Group. Study of heart and renal protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J.* 2010; 160(5): 785-794.e10. doi: 10.1016/j.ahj.2010.08.012

3. Cederberg H, Stancakova A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: A 6-year follow-up study of the METSIM cohort. *Diabetologia.* 2015; 58(5): 1109-1117. doi: 10.1007/s00125-015-3528-5

4. Arnaud C, Veillard NR, Mach F. Cholesterol-independent effects of statins inInflammation, immuno-modulation and atherosclerosis. *Curr Drug Targets Cardiovasc Haematol Disord.* 2005; 5(2): 127-134. doi: 10.2174/1568006043586198

5. Moghadasian MH. Clinical pharmacology of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor. *Life Sci.* 1999; 65: 1329-1337. doi: 10.1016/s0024-3205(99)00199-x

6. Unoki H, Takahashi A, Kawaguchi T, Hara K, Horikoshi M, Andersen G, et al. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet.* 2008; 40(9): 1098-1102. doi: 10.1038/ng.208

7. Mabuchi H, Higashikata T, Kawashiri M, Katsuda S, Mizuno M, Nohara A, et al. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. *J Atherosclerosis Thromb..* 2005; 12(2): 111-119. doi: 10.5551/jat.12.111

8. Salunkhe VA, Elvstam O, Eliasson L, Wendt A. Rosuvastatin treatment affects both basal and glucose-induced insulin secretion in INS-1832/13 Cells. *PLoS One.* 2016; 11(3): e0151592. doi: 10.1371/journal.pone.0151592

9. Aiman U, Najmi A, Khan RA. Statin induced diabetes and its clinical implications. *J Pharmacol Pharmacotherapy.* 2014; 5(3): 181185. doi: 10.4103/0976-500X.136097

10. Supale S, Li N, Brun T, Maechler P. Mitochondrial dysfunction in pancreatic β cells. *Trends Endocrinol Metab.* 2012; 23(9): 477487. doi: 10.1016/j.tem.2012.06.002

11. Wang C-H, Wang C-C, Huang H-C, Wei Y-H. Mitochondrial dysfunction leads to impairment ofinsulin sensitivity and adiponectin secretionin adipocytes. *FEBS J.* 2013; 280(4): 1039-1050. doi: 10.1111/febs.12096

12. Phielix E, Mensink M. Type 2 diabetes mellitus and skeletal muscle metabolic function. *Physiol Behav.* 2008; 94(2): 252-258. doi: 10.1016/j.physbeh.2008.01.020

13. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dosecompared with moderate-dose statin therapy: ameta-analysis. *JAMA.* 2011; 305(24): 2556-2564. doi: 10.1001/jama.2011.860

14. Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T. Effects of statins on theadipocyte maturation and expression of glucose transporter 4(SLC2A4): Implications in glycaemic control. *Diabetologia.* 2006; 49(8): 1881-1892. doi: 10.1007/s00125-006-0269-5

15. Manzoni M, Rollini M. Biosynthesis and biotechnological production of statins by filamentous fungi and application of these cholesterol-lowering drugs. *Appl Microbiol Biotechnol.* 2002; 58: 555-564. doi: 10.1007/s00253-002-0932-9

16. Schachter M. Chemical, pharmacokinetic and pharmacody-

namic properties of statins: An update. *Fundam Clin Pharmacol.* 2005; 19: 117-125. doi: 10.1111/j.1472-8206.2004.00299.x

17. Shepherd J. Who should receive a statin these days? Lessons from recent clinical trials. *J Intern Med.* 2006; 260: 305-309. doi: 10.1111/j.1365-2796.2006.01700.x

18. Sirvent P, Mercier J, Vassort G, Lacampagne A. Simvastatin triggers mitochondriainduced Ca2+signalling alteration in skeletal muscle. *Biochem Biophys Res Commun.* 2005; 329: 1067-1075. doi: 10.1016/j.bbrc.2005.02.070

19. Demyanets S, Kaun C, Pfaffenberger S, Hohensinner PJ, Rega G, Pammer J. Hydroxymethylglutaryl-coenzyme a reductase inhibitors induce apoptosis in human cardiac myocytes in vitro. *Biochem Pharmacol.* 2006; 71: 1324-1330. doi: 10.1016/j.bcp.2006.01.016

20. Sacher J, Weigl L, Werner M, Szegedi C, Hohenegger M. Delineation of myotoxicity induced by 3-hydroxy-3 methylglutaryl CoA reductase inhibitors in human skeletal muscle cells. *J Pharmac Exp Ther.* 2005; 314: 1032-1041. doi: 10.1124/jpet.105.086462

21. Cafforio P, Dammacco F, Gernone A, Silvestris F. Statins activate the mitochondrial pathway of apoptosis in human lymphoblasts and myeloma cells. *Carcinogenesis.* 2005; 26: 883-891. doi: 10.1093/carcin/bgi036

22. Paul DT, Gregory P, Amanda Z, Beth T. Statin-associated side effects. *J Am Coll Cardiol.* 2016; 67(20): 2395-2410. doi: 10.1016/j.jacc.2016.02.071