Hidroksi Metil Glutaril Coenzyme-A (HMG CoA) Reduktase Inhibitor and New Onset Diabetes Mellitus: A Review of Correlation and Clinical Implication

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Hidroksi Metil Glutaril Coenzyme-A (HMG CoA) Reduktase Inhibitor and New Onset Diabetes Mellitus: A Review of Correlation and Clinical Implication

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Abstract:
Treatment of lipid abnormalities with HMG CoA reductase inhibitor (statin) has been used for diabetic and non diabetic patients. Various studies have describe increased risk of new onset diabetes associated with statin therapy. This review aims to explain potential mechanism that related to diabetogenic effect of statin. This research was created by collecting literature that relevant to the topic. The types of literature used are clinical trials, meta analyzes and systematic reviews between 2013 until 2021. HMG CoA reductase is the target of statin therapy and the acting of this enzyme is inhibited by statin in competitive way. In vivo and in vitro studies reveal that statin reduce synthesis of mevalonate pathway and increase cholesterol transport that influence B cell function and decrease of insulin sensitivity and insulin secretion by multiple mechanism. Recent genetic study suggest that increased risk of type 2 diabetes mellitus pathway explained by gene variant target for LDL cholesterol lowering drugs. Accumulating evidence from several statin studies suggest that pravastatin is the least diabetogenic statin. Simvastatin, atorvastatin and rosurvastatin are more diabetogenic statin. The used of statin in clinical practice should concerned about benefit on cardiovascular while still considering the possible risk of developing type 2 diabetes mellitus. Regular monitoring of patients glycemic control is mandatory.

Keywords: diabetes mellitus; HMG-CoA reductase inhibitor; insulin resistance; statin

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, with a death rate of approximately 234 per 100,000 population. Inhibitors of 3-hydroxy-3-methylglutaryl - coenzyme A (HMG-CoA) reductase known as statins, are a therapy used in atherosclerotic cardiovascular disease (ASCVD) (Taylor, 2017). Statins have an important role in preventing cardiovascular events related to atherosclerotic lesions and blood lipids (Handelsman, 2020). In addition to these effects, there are pleiotropic effects of statins, such as ameliorative effects on systemic inflammation, endothelial function and oxidative stress (Oesterle et al., 2017).

Statins play a role in competitively inhibiting the HMG CoA reductase enzyme which plays a role in the cholesterol biosynthesis process by reducing intracellular cholesterol levels, the expression of LDL receptors on liver cells is upregulated, thereby increasing LDL clearance in the bloodstream. Statins lower cholesterol levels, stimulate more production of LDL receptors, stimulate the uptake of LDL cholesterol from the bloodstream, which ultimately contributes to reduced cardiovascular risk. If therapy is given aggressively with high intensity statins, it can reduce LDL cholesterol levels by >50% (Benjamin et al, 2017).

Statins are generally safe and well tolerated. However, in several studies statins were found to be associated with increased insulin resistance and the incidence of new-onset type 2 diabetes mellitus (NOD2). This association was demonstrated in a number of large cohort studies (Carter et al., 2013; Yoon et al., 2016; Casula et al., 2017; Angelidi et al., 2018; Ko et al., 2019), as well as in a meta-analysis of statin-related RCTs (Swerdlow, 2015; Thakker, 2016; Newman, 2019; Khan, 2019). A meta-analysis of randomized trials showed that higher intensity statin therapy with increasing doses was associated with an increased risk of NOD2 (Preiss et al, 2011). In addition, a study of genetic variants of the HMG-CoA reductase gene showed that reduced HMG-CoA reductase activity was associated with an increased risk of NOD2 (Ference et al, 2016). The use of statin therapy to reduce LDL cholesterol < 100 mg/dL or < 70 mg/dL is associated with an increased risk of NOD2 events of 16% or 33% respectively (Cai et al, 2014).

Several of the findings above raise awareness regarding the safety of long-term use of statins so that proper understanding and clinical consideration is needed regarding the risks of statin. Although the mechanism for lowering cholesterol by statins is widely known, as well as the various beneficial effects of statins, various studies have found an increased risk associated with the occurrence of new type 2 DM due to statins. The understanding regarding the mechanism by which statins cause diabetes mellitus is still not completely clear, so the author has created a review that will explain research studies and potential

mechanisms related to the effects of statins on cardiovascular disease and the risk of diabetogenic effects.

Methods

The method used to write this literature review is by collecting literature that is relevant to the topic raised, namely: Hydroxy Methyl Glutaryl (HMG) Coenzyme Reductase Inhibitor and Diabetes Mellitus. Literature was searched using the Pubmed search engine and Google search with the search keywords namely HMG-CoA Reductase Inhibitor and Diabetes Mellitus or Statins in Diabetes Mellitus.

The type of literature used are meta-analysis, clinical trials and systematic reviews. The literature search was taken from 2013 to 2021. The literature selected and included consisted of 25 articles originating from Google Scholar and Pubmed.

Result and Discussion

HMG-CoA Reductase Inhibitor Mechanism

Statins are reversible and competitive inhibitors of HMG-CoA reductase, which is a rate-determining enzyme in the cholesterol biosynthesis pathway. The HMG-like moiety of statins, which is the modified 3,5-dihydroxyglutaric acid moiety, is structurally similar to HMG-CoA and causes inhibition of the HMG-CoA reduction reaction. Through this mechanism, the mevalonate pathway is inhibited along with a consequent reduction in downstream products and cholesterol synthesis **(Figure 1A)**. In addition, this statin-mediated decrease in intracellular cholesterol levels leads to upregulation of LDL receptors (LDLR) in the liver and peripheral tissues, resulting in a decrease in blood LDL cholesterol (LDL-C). LDLR is the main route by which LDL-C is removed from the circulation, and its synthesis has been shown to be inversely correlated with the amount of cholesterol synthesized by cells (Jahanshahi et al, 2009). Through the action of statins, cellular cholesterol concentrations decrease, stimulating the production of more LDLR and favoring the removal of LDL-C from the bloodstream, ultimately reducing the risk of CVD (Fong, 2014).

Statins are classified according to their hydrophobicity into hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin and simvastatin). The solubility and pharmacological properties of statins are determined by the substituents in the ring attached to the active site. Hydrophilicity comes from polar substituents added to the active site while the addition of nonpolar substituents causes lipophilicity **(Figure 1B)** (Fong, 2014).

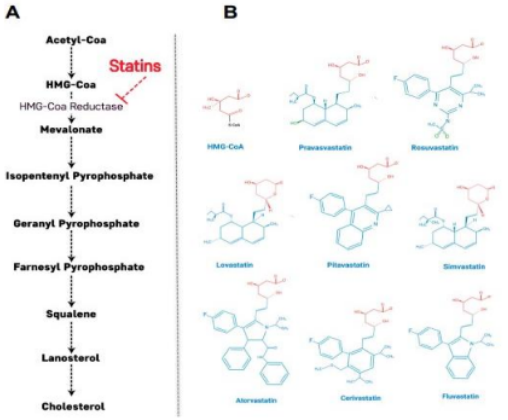

Figure 1. Statin-induced inhibition of the mevalonate pathway and structure of statins. **(A)** Inhibition of HMG-CoA reductase significantly blocks the production of mevalonate, a necessary precursor for cholesterol synthesis. Mevalonate is the building block for a variety of other compounds. **(B)** Structural formula of statins and HMG-CoA. The HMG-like moiety (in red) is conserved in all statins. The polar substituents responsible of pravastatin and rosuvastatin are colored in green (Fong, 2014).

Although the target of both types of statins is HMG-CoA reductase, the mechanisms of inhibition are different. Hydrophilic statins target the liver more efficiently because their absorption is carrier-mediated, whereas lipophilic statins passively diffuse through hepatocellular membranes and are also able to diffuse in extrahepatic tissues, thereby exhibiting reduced hepatoselectivity. Their diffuse influence on extrahepatic tissues may explain the higher incidence of side effects observed with lipophilic statins. An exception to this is rosuvastatin, which is a hydrophilic statin but has a similar activity profile to lipophilic statins (Fong, 2014).

HMG-CoA Reductase Inhibitor and New Onset Diabetes Mellitus Tipe 2 Risk

Several studies show an association between statin therapy and the risk of type 2 diabetes mellitus. Research conducted by Sattar et al (2010) in 91,140 subjects showed an overall 9% increased risk from 13 RCTs for 4 years of statin use (odds ratio [OR] 1.09; 95% CI 1.02–1.17). In research conducted by Preiss et al (2011) in 32,752 subjects reported a significant increase in the incidence of diabetes with intensive dose statin use compared with moderate dose use (OR 1.12; 95% CI 1.04- 1.22) for a mean of 4.9 years of use (Preiss et al, 2011).

A meta-analysis conducted by Navarese et al. (2013) on 113,000 subjects covering 17 RCTs. A study compared the incidence of new-onset diabetes in patients receiving statins and placebo with high-dose and medium-dose statins. In this study, the lowest risk was found when using pravastatin 40 mg compared to placebo (OR 1.07; 95% CI 0.83-1.30), then using atorvastatin 80 mg had an intermediate risk (OR 1.15; 95% CI 0 .9-1.50) and use of rosuvastatin 20 mg had the highest risk (OR 1.25; 95% CI 0.82-1.90). However, none of these differences reached statistical significance. Simvastatin is associated with a higher risk compared with pravastatin (Navarese, 2013).

Latest clinical and population studies found that in individu with type 2 diabetes mellitus, high intensity atorvastatin for 10 weeks increase insulin resistance and insulin secretion. Overtime, the risk of new onset of diabetes with statin used may increased in individu who became more insulin resistance but are unable to maintain compensatory increase of insulin secretion (Abbasi, 2021).

Several studies show factors that influence the relationship between statins and diabetes (Preiss et al, 2011; Navarese, 2013; Sattar et al, 2010), as described below:

- Use of hydrophilic vs lipophilic statins.
  Hydrophilic statins include pravastatin, rosuvastatin. Lipophilic statins include atorvastatin, lovastatin, simvastatin. Studies show that lipophilic statins have an influence on blood sugar levels and HbA1c.
- The dose size and duration of LDL cholesterol reduction in high risk patients.
  However, a meta-analysis in 2011, involving 32,752 patients without diabetes from 5 clinical trials of statins, showed an increased risk of incident diabetes compared with moderate-dose statin therapy, namely a 0.8% absolute increase in diabetes events and a 2.6% absolute reduction in cardiovascular events on high-dose statins.
- Age or clinical characteristics of the population.
  A meta-analysis showed the risk of diabetes with statins was higher in older patients, but was not influenced by body mass index or how long LDL cholesterol was lowered (Sattar et al, 2010).

HMG-CoA Reduktase Inhibitor induced Diabetes Mellitus

Statins lower cholesterol and risk of CVD, but at the same time, may increase blood glucose and risk of NOD. The exact mechanisms between the opposing effects of statins on lipids versus glucose are still unclear. It is known that statins have cholesterol-independent pleiotropic effects that influence both insulin and glucose control. A number of potential deleterious effects of statins on β cell function have been proposed, including the effects of increased influx of cholesterol due to inhibition of HMGCoA-mediated intracellular cholesterol synthesis, inhibition of ubiquinone (CoQ 10) synthesis leading to mitochondrial oxidative stress, and β cell apoptosis (Sampson et al, 2011). It has been proposed that chronic statin treatment increases gluconeogenesis by upregulating gene expression of key enzymes that increase glucose production in the liver. Additionally, it has been shown that statins can impair the insulin signaling pathway as well as downregulate the GLUT-4 transporter, which is responsible for the uptake of glucose in peripheral cells. Statins can also induce changes in circulating free fatty acids (FFA), changes in hormones such as adiponectin and leptin, impairment of β-cell function, β-cell damage, and adipocyte maturation/differentiation. Additional mechanisms involving epigenetic regulation mediated by specific microRNAs have also being involved in the reduction of insulin secretion. These complex pathophysiologic molecular mechanisms of statininduced NOD are summarized in **Figure 2 (**Galicia-Garcia et al, 2020**)**.

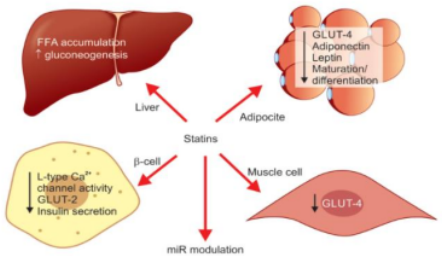

Figure 2. Principal proposed mechanisms for statin-induced NOD. (FFA: free fatty acis; GLUT: glucose transporter; NOD: new onset diabetes) **(**Galicia-Garcia et al, 2020**)**

Recently, it has been suggested that statin-induced activation of the NLRP3 (NOD-, LRR- and pyrin domaincontaining protein 3) inflammasome contributes to insulin resistance (**Figure 3**). Although, the pleiotropic effects of statins are thought to be largely anti-inflammatory, activation of the NLRP3 inflammasome promotes adipose tissue inflammation, which can precipitate insulin resistance (Henriksbo et al, 2020). In the first step known as priming, transcriptional events induced by nuclear factor kappa B (NF-κB) following pattern recognition receptor (PRR) stimulation increase levels of inflammasomes like NLRP3 and inflammasome effectors like pro-IL-1beta. This leads to immune activation where inhibition of HMGCR with statins decreases protein prenylation, triggering signals that promote NLRP3 inflammasome activity.

Also, statins cause variety of other effects including promotion of intracellular adenosine triphosphate (ATP) release, which promotes potassium efflux, a key trigger for increased NLRP3 inflammasome activity. This activity causes cleavage of pro-IL1beta into active IL-1beta by caspase-1, promoting metabolic modulation. IL-1beta-mediated inflammation and activation of mitogen-activated protein kinase (MAPK) inhibit insulin signaling either at receptor substrate-1 level (IRS1), or through an unknown target of caspase-1 that inhibits downstream signaling through a suspected number of pathways (Azemawah et al, 2019).

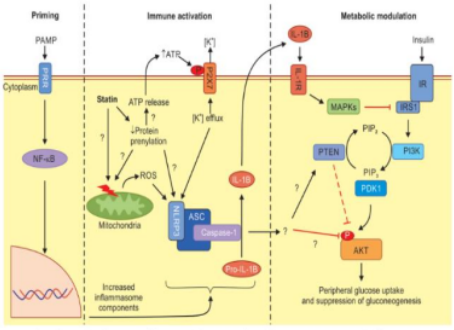

Figure 3. Statin-induced activation of the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome contributes to insulin resistance (Galicia-Garcia et al, 2020).

Recently, parallels have been drawn between the dysregulation of insulin producing β-cells and insulin resistance in adipocytes caused by statin lowering of isoprenoids (Henriksbo et al, 2020). Statins may engage a similar isoprenoid-mTOR mechanism to promote cholesterol independent side effects in insulin producing cells and insulin-responsive cells. Thus, it appears worthwhile to further investigate the role of m-TOR-NLRP3 pathway and restoring specific isoprenoids to mitigate glycemic side effects of statins.

HMG-CoA Reduktase Inhibitor and Clinical Implication

Aggressive treatment of lipid abnormalities with statins as the primary drug has generally been used as the standard of care for diabetes patients, especially in patients with cardiovascular disease or 1 or more risk factors. Statins should be used after assessing the risks and benefits. Primary prevention patients at moderate and high risk and secondary prevention patients are not stopped or the dose is reduced based solely on concerns about the development of diabetes. Apart from these groups, the use of statins should only be limited to patients with significant increases in LDL cholesterol with the target of non-aggressive LDL cholesterol reduction, as well as regular monitoring of the patient's glycemic control parameters (Rocco, 2012; Sattar et al, 2010).

Conclusion

Various studies have described the diabetogenic effects of statins. Various clinical evidence supports that statins increase the risk of type 2 DM, especially certain types of statins (simvastatin, rosuvastatin, atorvastatin). The mechanism of the diabetogenic effect of statins is not completely clear, however, it is thought to be related to insulin secretion and resistance. The use of statins in clinical practice should concerned about the benefits and cardiovascular risks while still considering the possible risk of developing type 2 DM.

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Conceptualization, methodology, writing—original draft preparation, writing—review and editing by author. Authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest
The authors declare no conflict of interest.

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