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Review Article:

Comprehensive Approaches to the Effect of Statins on Glucose Homeostasis

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Abstract

Background: Disturbance in glucose tolerance is a significant risk factor for cardiovascular diseases. Statins are commonly prescribed to lower cholesterol levels, but their potential effects on glucose tolerance and induction of type 2 diabetes have drawn attention. **Aim:** This review highlights the connection between statin medications and glucose homeostasis. **Methods:** An extensive literature search has been conducted on various electronic databases such as PubMed, Scopus, Web of Science, and Science Direct. **Conclusions:** Different mechanisms are hypothesized and could be responsible for this pleiotropic effect of statins on glucose homeostasis. Many clinical trials and meta-analyses have reported a significant controversy regarding statins-induced glucose tolerance/intolerance depending on the type of statin and dosage. This urges the researchers to perform more studies to clarify this pleiotropic effect for each statin. Although the present knowledge regarding the impact of statins on glycemic index has been improved, several molecular/cellular aspects are yet to be determined.

1. Introduction

In 1971, Japanese biochemist Akira Endo created the first statin. Since then, statins have been one of the most prescribed drugs globally (1). These statins are well tolerated, safe, and have few adverse effects (2,3). Most of the cholesterol seen in the plasma comes from the internal synthesis that occurs in hepatocytes rather than from the food (4).The most important mechanism of action of statins is by blocking an essential step in the hepatic cholesterol manufacturing process via inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-COA) reductase, which lowers the synthesis of mevalonic acid. This reduced intracellular cholesterol concentration induces the synthesis of LDL receptors in hepatocytes to stimulate hepatic LDL reuptake from the circulation (5). As a result, statins are one of the most effective medications for preventing atherosclerotic coronary heart disease (6). They also lower blood triglycerides, decreasing their cardiovascular (CV) risks attributed to their atherogenic dyslipidemia (7). Based on their effectiveness and potency in reducing LDL levels, statins can be categorized as follows: the first generation comprises fluvastatin, pravastatin and lovastatin; the second generation includes simvastatin and atorvastatin, while rosuvastatin and pitavastatin are among the third-generation (**Figure 1**) (8). According to their solubility in either water or lipid-containing media, statins are often divided into hydrophilic and lipophilic categories, respectively. Hydrophilic statins (pravastatin and, to a lesser degree rosuvastatin) have higher hepatoselectivity and stay attached to the membrane's polar surface, and need protein transporters to enter the cell to block the HMG-CoA reductase enzyme. Therefore, the capacity of hydrophilic statins to have non-LDL effects at extrahepatic locales may be diminished by the liver–specific, and carrier-mediated mechanisms that are necessary for their uptake. Whereas the lipophilic statins (simvastatin, atorvastatin, pitavastatin, fluvastatin, and lovastatin) can act intracellularly by interact with the nearby acyl chains after passing into the membrane (8). Lipophilic statins can enter extrahepatic cells and prevent the production of isoprenoid and coenzyme Q10 (CoQ10), which are mevalonic–derived compounds (9). The elimination of statins is also influenced by solubility, as

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lipophilic statins are metabolized by the membrane-bound cytochrome P450 (CYP) enzyme, but hydrophilic atorvastatin is substantially removed unaltered (8).

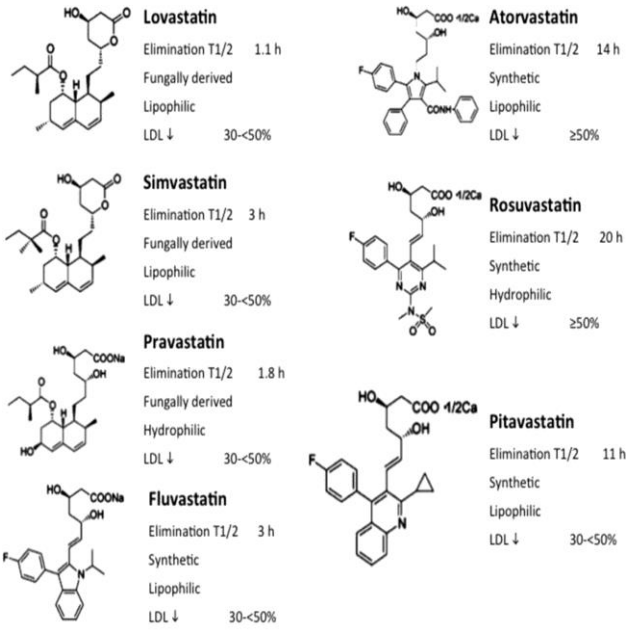

Figure 1. Structures and pharmacokinetic properties for different statins (10).

On the other hand, several side effects have been reported due to statin use including myopathy, rhabdomyolysis, elevated liver enzymes, and acute renal failure. However, the most frequent adverse effect of statins is myalgia, with reported rates ranging from 1 to 10% (11).

The most dangerous side effect of using statins is rhabdomyolysis, which happens very infrequently (less than 0.1%). Alcohol abuse, polypharmacy, and hypothyroidism are the most prevalent risk factors for statin-related myopathy. Up to 1% of individuals using statins experience abnormal results on liver function tests. However, the clinical relevance of this is unreliable (12). It has been hypothesized that fasting blood glucose levels were significantly elevated due to statins therapy, leading to an increased risk of new-onset diabetes mellitus (NODM) and increased rates of insulin resistance in individuals with preexisting impaired glycemic control. In addition, the researcher hypothesized that an increased statin dosage correlates with an intensified diabetogenic impact (13,14). This review aims to investigate the potential impact of statin medications on glucose homeostasis. Statin medication has been linked to a marked increase in fasting blood glucose levels, which has been hypothesized to raise the likelihood of developing new-onset diabetes mellitus (DM) and insulin resistance in people who already have impaired glycemic control.

2. Methodology

Several high quality databases have been utilized in this review such as the PubMed (National Institutes of Health, National Library of Medicine), EMBASE, Scopus, Web of Science, and Science Direct databases. These database were chosen because of their comprehensive coverage, search functionality and containing high-quality, peer-reviewed journals to ensure the information gathered is credible and reliable. The examination of databases for studies encompassed the terms “statin”, “atorvastatin”, “pravastatin” or “rosuvastatin” or “pitavastatin” or “cerivastatin” or “lovastatin” or “fluvastatin”, “HOMA-IR”, “ glucose homeostasis model insulin resistance”, “glycated hemoglobin”, “HbA1c” and/or “AKT” within the title or abstract. The inclusion criteria involved researches published in English and conducted on humans, namely adults, and animals. Furthermore, exclusion criteria involved studies involving individuals with organ transplants, or renal disease, as these disorders influence glycemic management (de Leo et al., 2000; Muller et al., 2021). This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Moher et al., 2010). In addition, to ensure a comprehensive view on the effect of statins on glucose metabolism, different designs of study were included in this review such as randomized Controlled Trials (RCTs), observational studies, Meta-analyses, and both in-vivo and in-vitro Studies.

3. Pleiotropic effect of statins

The synthesis of cholesterol is strongly inhibited by statins. In clinical trials, statins have demonstrated benefits in primary and secondary prevention of coronary heart disease. Nevertheless, the overall advantages of statins seem to exceed the substantial benefits of lipid-lowering effect (15).Statins have cholesterol-independent “pleiotropic “effects **Figure 2**. such as they can improve endothelial function, increase the stability of atherosclerotic plaques, reducing oxidative stress and inflammation, and decrease thermogenic response. Moreover, statins have extrahepatic advantages on the CNS, immune system, and bone (16,17).

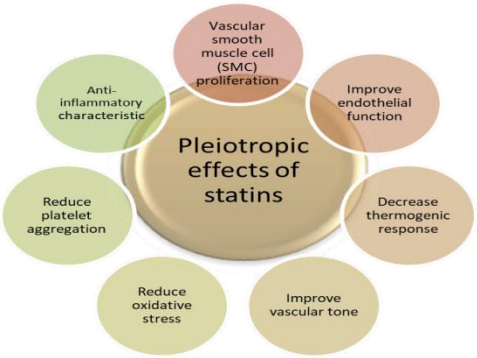

Figure 2. Pleiotropic effects of statins.

The cardiovascular disease (CVD) is currently the most prevalent non-communicable disease worldwide in terms of morbidity and mortality. Evidence from mechanistic and genetic studies indicates that low-density lipoprotein cholesterol (LDL-C), which contains ApoB, is the causative agent of atherogenesis (10). Statins are effective in preventing coronary heart disease (18). Reduced hepatic cholesterol production may be the cause of decreased gallstone formation. Lower cholesterol also reduces platelet aggregation and consequently may prevent deep vein thrombosis and slow the progression of renal disease by reducing renal artery atherosclerosis (10,17).

In patients with sinus rhythm, statins could be significantly linked with a decreased risk of atrial fibrillation (20). In addition, statins decrease recurrent angina episodes following acute coronary events and raise myocardial perfusion (21). Endothelial dysfunction is defined as a lack of endothelium-derived nitric oxide (NO), which is measured as a poor vasodilatory response to different stimuli (22). Satins reduce cardiomyocyte resting tension, decrease endomyocardial inflammation, and enhance NO bioavailability through tetrahydrobiopterin (BH4)-mediated endothelial NO synthase (eNOS) recoupling (23). In order to prevent endothelial dysfunction, it has been previously discovered that statins suppress the ectopic expression of miRNA-133a in vascular endothelial cells by targeting GTP cyclohydrolase (24). Statins can reduce oxidative stress in the heart, and blood vessels, and have anti-inflammatory effects (25). According to a review by Wang et al., (2007), numerous studies have demonstrated that statins inhibit the action of angiotensin II, limit sign transmission from membrane receptors, slow down the remodeling of the heart, and blood vessels, and stop the apoptotic process (26).

In addition to their well-known effects in decreasing cholesterol, statins have a major effect on vasomotor function, which includes vasorelaxation and vasoconstriction. Statins can improve endothelial function in different ways, including the upregulation of endothelial nitric oxide synthase (eNOS), which raises NO production. This action lowers vascular resistance and enhances endothelium-dependent vasodilation (25,26). Furthermore, cardiovascular vasoconstriction has been shown to be diminished by statins. Statin therapy can reduce the impact of coronary spasms and enhance overall vascular reactivity in patients with vasomotor disorders (29). These results highlight the great cardiovascular advantages of taking statin therapy in addition to the cholesterol control.

3.1. Glucose homeostasis

Glucose homeostasis (or glucose tolerance) is described as the ability to metabolize exogenous glucose and preserve normal blood sugar levels whereas glucose intolerance is defined as a reduced capacity for glucose disposal (30). The levels of blood glucose are strictly maintained within a small physiological range to prevent hypoglycemia and hyperglycemia which could be fatal. The equilibrium between the liver's synthesis of glucose and the use of glucose by insulin-dependent tissues (like muscle and fat) and non-insulin dependent tissues (such as the brain) is necessary for glucose tolerance (31). Other important factors determining glucose tolerance include the ability of pancreatic beta cells to release insulin (also known as acute insulin response to glucose or beta cell responsiveness), the capacity of insulin to prevent the liver from producing glucose, and the encouragement of peripheral tissue to use it (also known as insulin sensitivity).

Type 2 diabetes is one of the most common metabolic diseases, commonly referred to as T2DM. The two main causes of it are the inability of insulin-sensitive tissues to react appropriately to insulin in addition to the defective production of insulin by pancreatic β-cells. There is strict regulation over the molecular processes that produce, release and detect insulin. This is because insulin activity and release are crucial mechanisms for preserving glucose homeostasis. If there are dysfunctions in any of the mechanisms underlying these processes, a metabolic imbalance may result in the disease's onset (32).

Laboratory tests such as oral glucose tolerance test (OGTT) ≥ 200 mg/dl two hours after a 75 g oral glucose load, fasting blood glucose ≥ 126 mg/dl ,and glycated hemoglobin (HbA1c) > 6.5%, can be used to diagnose diabetes mellitus (33). Tolerance to glucose is measured using the oral glucose tolerance test, which involves consuming a glucose solution and monitoring glucose levels at regular intervals over the next two hours. Glucose tolerance can also be assessed after ingesting a carbohydrate-rich meal or after receiving an intravenous injection or infusion of glucose (34). The test is helps examine post-prandial responsive hypoglycemia, the equivocal diagnosis of T2DM, and gestational diabetes mellitus (GDM) (35). OGTT is recommended for pregnant women who have never been diagnosed with diabetes mellitus (DM), and who are between weeks 24 and 28 of gestation (28,36). It has good sensitivity for DM diagnostic screening, although it should ideally be used to diagnose DM in patients who are pre-diabetic or who have risk factors for the disease, such as obesity, a family history of DM, a previous diagnosis of GDM, or polycystic ovaries (37).

3.2. Statins and glucose homeostasis

Statins have been shown to impact glucose regulation in several ways, including influencing β-pancreatic cells' synthesis and secretion of insulin, insulin resistance, muscle and adipocyte uptake of insulin, and adipokine production (38). According to existing data, the majority of statins have negative side effects on the ability of diabetic patients to control their blood sugar levels. The LDL-C receptors in the pancreatic β cells increased their uptake of LDL-C as a result of statins' inhibition of de novo synthesis of cholesterol. This led to an increase in the production of plasma-derived LDL-C, which differed significantly from de novo synthesized cholesterol in several important ways (39,40).

A vital cellular metabolic process, the mevalonate pathway, also known as the HMG-CoA reductase pathway, is essential for the synthesis of sterol isoprenoids like cholesterol and non-sterol isoprenoids (41). Statins can affect and lower glycemic control because they inhibit the production of several metabolites that are considered determining factors in glucose uptake and insulin secretion and are typically produced during cholesterol synthesis in the mevalonate pathway such as isoprenoids, geranylgeranyl pyrophosphate (GGPP), farnesyl pyrophosphate (FPP), and ubiquinone (coenzyme Q10, CoQ10) **Figure 3**, (42,43). Research has been performed on the possible protective effects of coenzyme Q10 (ubiquinone) against different drug-related adverse effects (44,45). Coenzyme Q10 has a role in mitochondrial energy synthesis. Statins lower levels of CoQ10, which may be the reason why adenosine triphosphate (ATP) is produced less frequently. Consequently, this impacts the energy balance of the cells and the release of insulin by the beta cells in the pancreas. A drop in ATP levels can interfere with the signaling required for insulin to work effectively, which can further complicate glucose metabolism (46).

In addition, the glucose transporter 4 (GLUT4) is known to enhance glucose uptake when isoprenoids (FPP and GGPP) are present. Insulin resistance would result from GLUT4 downregulation, which would also affect insulin action (47). Furthermore, statins may also affect downstream signaling cascades and the insulin receptor substrate (IRS), both of which are critical for GLUT4 translocation to the plasma membrane, hence exacerbating insulin resistance (48).

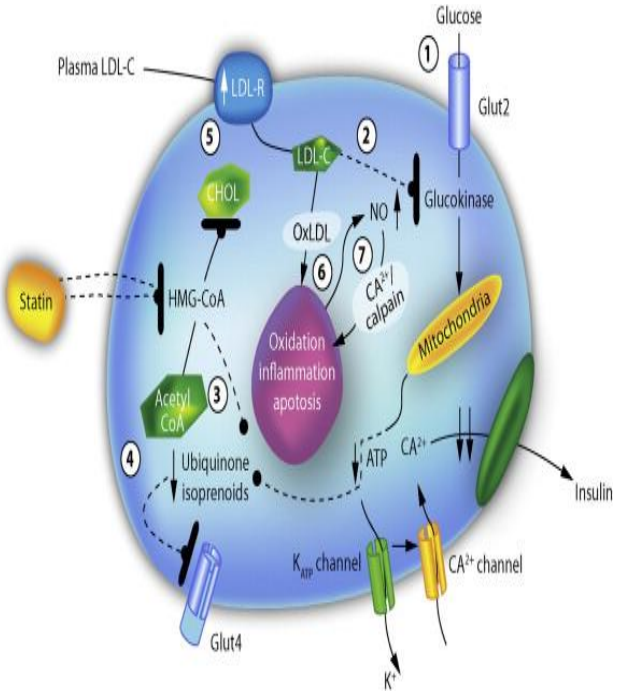

Figure 3. Diagram for statin-induced disruption of glucose metabolism (49)

Usually, beta cells produce insulin in response to elevated blood glucose, a process that is dependent on Ca^{+2}. Insulin secretion depends on cholesterol in the beta cell's plasma membrane, and consequently, reducing cholesterol levels lowers glucose-stimulated insulin release by more than 50% (50). Therefore, it is necessary to strictly regulate the balance between the circulating and cellular levels. It is still unclear if statins affect glucose metabolism directly by affecting beta cells or through this state of equilibrium (51).

A cohort follow-up study revealed a link between statin use and an increased risk of diabetes as well as decreased insulin sensitivity and secretion (52). Furthermore, as atorvastatin was consistently diabetogenic and pravastatin was only diabetogenic in insulin-resistance people, it has been suggested that there were differences in the diabetogenic effects of two general categories of statins (lipophilic vs hydrophilic). The dosage of statin therapy needs to increase continuously as dyslipidemia worsens. Determining whether this statin dosage has an increasing impact on glycemic control is therefore intriguing. There is differentiation noted between the various forms of statins when discussing their diabetogenic effects (53,55).

Cui et al., (2018) performed a network meta-analysis of 23 trials to assess the overall effects of statin and statin dosage on hemoglobin A1c. Overall, in statin users, hemoglobin A1c increased by 0.11%. The greatest impact was with high-intensity atorvastatin, which causes LDL reduction of ≥ 50% in comparison with low or moderate intensity statins(56). It was associated with a mean increase of 0.63% while pitavastatin was associated with a reduction in hemoglobin A1c compared with all other statins (57). The Fremantle Diabetes Study, an observational study in Australia, found that low-intensity statins were not associated with any change in hemoglobin A1c. However, moderate-intensity statins were associated with a mean increase of 0.22% (P = 0.022); and high-intensity statins were associated with a mean increase of 1.05% (P = 0.023) (58).

Lifestyle factors and patient-specific characteristics are crucial for the statins-glucose homeostasis relationship. In terms of lifestyle factors effect, since regular physical activity and weight management can enhance insulin sensitivity and glucose metabolism, exercise and weight loss can counteract the disadvantageous effect of statins on glucose levels. Additionally, type of diet is crucial in regulating plasma glucose level as high refined carbohydrates can enhance insulin resistance and counteract the benefits of statin therapy. Furthermore, smoking can increase the risk of developing T2DM in patients taking statins, by further enhancing the metabolic effects induced by statins (13).

Furthermore, the evidence that statins increase the risk of type 2 diabetes is not consistent between all populations. It is higher among older patients as research suggests that older adults on high-intensity statin therapy are even more vulnerable to type 2 diabetes than younger people (59). Physiological changes including insulin sensitivity and pancreatic function naturally deteriorate with age, and statin medication may make these declines worse (60). Besides, there are some other factors that raise this risk such as pre-existing conditions: comorbidities including obesity or metabolic syndrome put older adults at risk for diabetes (54). So choosing the right statin kind and dosage should be considered for those who are at risk of type 2 diabetes.

3.3. Rosuvastatin and glucose homeostasis

Rosuvastatin is a new generation of HMG-CoA reductase inhibitor. It has various unique pharmacologic and pharmacokinetic characteristics such as it has little extrahepatic tissue penetration, low potential for CYP3A4 interactions, and substantial LDL-C lowering effect (61). Recent research trials investigated the potential benefit of this medication in both the prevention and treatment of cardiovascular disease in many populations, such as those with heart disease, kidney disease, DM, and older people, as well as its effect in combination with other lipid-lowering medications (61). The lipophilicity of rosuvastatin is higher than that of pravastatin, but it is lower than that of other statins like atorvastatin and simvastatin (61,62).

Salunkhe et al., (2016) found a dual effect of rosuvastatin on glucose homeostasis in mice, both those on a normal diet (ND) and those on high-fat diet (HFD). In ND mice, rosuvastatin was able to reduce blood glucose levels through improved insulin sensitivity and increased glucose uptake in adipose tissue. However, rosuvastatin has another effect which is lowering insulin secretion and insulin content in islets when it was tested in vitro. The administration of rosuvastatin resulted in an impairment of Ca^{2+} signaling in beta cells, as well as an increase in the density of granules at the plasma membrane. It was shown that treatment with rosuvastatin led to a reduction in the release of compensatory insulin and an increase in the uptake of glucose (51).

A prospective randomized controlled trial conducted on prediabetic individuals showed that 10 mg rosuvastatin treatment daily for 6 months could decrease insulin sensitivity and increase insulin resistance (64). However, one year of 20 mg rosuvastatin treatment daily to type 2 diabetic patients led to impairment of glucose homeostasis and insulin secretion with no effect on insulin sensitivity. Additionally, rosuvastatin reduced inflammation, as well as enhanced endothelial function (65). So the previous studies showed different effects of rosuvastatin on glycemic control depending on the dose and duration of the treatment.

Rosuvastatin significantly raised HbA1c levels by 1.44% on average in the majority of studies in the sub-analysis of statin types. While the effects of rosuvastatin were not significant in those who had a high HbA1c or blood sugar level. In both people with normal HOMA-IR (below 2.15 (1.44 ± 0.44)) and subjects with initial high HOMA-IR (over 2.15 (3.45 ± 1.16), this marker of type 2 diabetes was considerably elevated by the presence of rosuvastatin (66).

3.4. Atorvastatin and glucose homeostasis

Patients with hypercholesterolemia and patients with hypertriglyceridemia have been reported to experience dose-dependent reductions in total cholesterol, low density lipoprotein(LDL)-cholesterol, and triglyceride levels when they are treated with atorvastatin (67).

As a lipophilic statin, atorvastatin has been shown to have adverse effects on glucose metabolism, especially in people who have diabetes or glucose intolerance. A study found that atorvastatin reduced the glucose level by suppressing the expression of Glucokinase (GCK), and GLUT2 in the liver (68). Additionally, atorvastatin may lower the amount of the GLUT4 protein in adipocytes and prevent them from absorbing glucose. Moreover, by suppressing and altering skeletal muscle function, atorvastatin may also increase the risk of developing diabetes (Sun et al., 2018). According to Watson et al. (2006), GLUT4 expression and mobility are regulated by a variety of factors, such as mitogen-activated protein kinase (MARK) signals and protein kinase C isoform (PKCs) (69) . However, the precise mechanism by which statins modify GLUT4 gene transcription and function is still unknown.

Cederberg et al., (2015) discovered that there is dose-dependent insulin secretion and insulin resistance when utilizing simvastatin and atorvastatin (52). Most studies and clinical investigations demonstrated that high-dose atorvastatin increased the incidence of new onset-diabetes more than lesser doses (54). A slightly increased incidence of new onset of diabetes was linked to atorvastatin at moderate dosage. A clinical research study demonstrated a risk ratio of 1:10 for people taking atorvastatin 10 mg vs 80 mg (70,72).

Moreover, the use of atorvastatin for a short period disrupts glucose homeostasis and inhibits LDLR expression in pancreatic islets in mice, indicating the importance of addressing the involvement of LDLR in the diabetogenic effect of statins through additional research (73). However, long-term treatment with atorvastatin did not have an effect on

glucose homeostasis in rabbits with normal blood cholesterol levels (74). More research is required to find the effect of the duration of treatment of atorvastatin on glucose homeostasis.

Atorvastatin was shown to cause a substantial increase in HBA1c, with a mean difference of 0.24% when the participants had normal HbA1c readings below 6.5% (5.78± 0.28). If the patients have HbA1c values greater than 6.5% (7.71± 1.53), a substantial increase in HbA1c level was produced with a mean difference of 0.26%. HOMA-IR index was significantly elevated as a result of the administration of atorvastatin in both people with normal and high HOMA-IR (66) .

3.5. Simvastatin and glucose homeostasis

Simvastatin is the most commonly prescribed lipophilic statin since it effectively reduces LDL lipoprotein cholesterol levels, and lowers the risk of cardiovascular disease and death (75). It is a semi-synthetic counterpart of lovastatin made from fermented Aspergillus terreus (76). Simvastatin is typically administered to patients at doses of 10, 20, or 40 mg daily; however, because of the elevated risk of muscle damage, the use of 80 mg/day has been prohibited (77).

High dosages of simvastatin may have unfavorable pleiotropic effects, including a reduction in insulin secretion (75,76). It has been postulated that simvastatin reduces insulin secretion by limiting the rise of free [Ca^{2+}] in the cytoplasm (39). According to a study by Yada et al., (1999), simvastatin inhibits β cell L-type Ca^{2+} channels and reduces insulin release. After 20 seconds of simvastatin injection, the amount of insulin released by L-arginine and potassium chloride was decreased (79). Islet β cell lines of MIN6 mice have been used to explain how simvastatin affects the secretion of insulin. When compared to normal control cells, simvastatin significantly decreased insulin production in a dose-related manner. Insulin secretion was indirectly suppressed as a result of lower glucose transporter 2 (GLUT2) levels. Simvastatin reduced the levels of adenosine triphosphate (ATP) in MIN6 cells, while simultaneously increasing the current in ATP-sensitive potassium channels (KATP) and decreasing the L-type Ca^{2+} current. Simvastatin may also reduce insulin secretion by inhibiting membrane cell depolarization and calcium influx by raising the rectifier potassium channel current and lowering voltage-dependent Ca^{2+} channel 1.2 current (80). Additionally, the Study of Effectiveness of Additional Reductions in Cholesterol, Homocysteine (SEARCH) trial found that a slightly greater incidence of new-onset diabetes was caused by high dosages of simvastatin (80 mg/day; 11.6%) compared to low doses (20 mg/day; 10.9%) (2).

On the other hand, several investigations found that insulin levels were either increased or unchanged due to simvastatin use (77,78). Simvastatin did not increase HbA1c when administered to individuals whose blood glucose levels were normal and in those with high HBA1c values exceeding 6.5% (66). In addition, the HOMA-IR index was significantly elevated as a result of the administration of simvastatin in both people with normal and high HOMA-IR (66). Another study found that simvastatin can affect glucose homeostasis via PGC-1α expression which is a regulator of mitochondrial biogenesis and muscle energy metabolism. In wild-type and PGC-1α Knockout (KO) mice, simvastatin was found to negatively impact skeletal muscle insulin sensitivity whereas in PGC-1α overexpressing mice, it enhanced the uptake of glucose by the muscle (83).

3.6. Pravastatin and glucose homeostasis

Pravastatin is a first-generation statin that is used in the treatment of people who are at risk of developing cardiovascular disease. Pravastatin is a competitive inhibitor of hydroxymethyl glutaryl CoA reductase leading to increasing the expression of hepatic LDL receptors, which in turn results in a reduction in levels of LDL cholesterol in the bloodstream (84). Pravastatin is a very hydrophilic statin that is transported by certain organic anion transporters across hepatic cell membranes. It has poor systemic bioavailability and hepato-selectivity.

The West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated a significant reduction in the risk of developing type-2 diabetes in hypercholestremia patients treated with pravastatin (85). When pravastatin was administered to rats who were genetically susceptible to acquiring diabetes mellitus an increase in glucose metabolism and a reduction in glucose intolerance occurred. In addition, Otani et a., (2010) suggested a preventive and therapeutic effect of pravastatin on the progression of DM and pancreatic fibrosis via exerting anti-inflammatory, anti-oxidative, and anti-fibrotic effects in the OLETF rat (86). Early pravastatin treatment in a rat model of spontaneously emerging type II diabetes blocked coronary artery remodeling and left ventricular diastolic dysfunction while also delaying the formation of new DM. Therefore, they could be used to avoid cardiovascular problems in a population at risk of developing diabetes mellitus (87).

Another study found that the dose of pravastatin is critical to modulate glucose homeostasis. The authors concluded that pravastatin, especially at the dose of 20 mg/kg/day is more effective in modulating carbohydrate metabolism and consequently, in ameliorating the negative effects of DM (88). In Alvarez-Jimenez et al., (2023),

pravastatin did not result in an increase in the level of blood glucose for those with normal blood glucose levels and in people with HBA1c values higher than 6.5%. Additionally, pravastatin decreased HOMA-IR in normal individuals. In contrast, pravastatin was found to significantly increase HOMA-IR in those individuals who had initial HOMA-IR values that were greater than 2.15(66).

3.7. Pitavastatin and glucose homeostasis

The FDA approved pitavastatin as adjuvant therapy for primary and mixed dyslipidemia, helping to increase HDL and decrease total cholesterol, low-density lipoprotein cholesterol (LDL), apolipoprotein B (Apo B), triglycerides (TG), and low-density lipoprotein cholesterol (LDL) (85,86). It has been approved to treat children older than eight years who have heterozygous familial hypercholesterolemia (HeFH) (91).
According to the hazard ratio (HRs') meta-analysis, pitavastatin significantly decreased the incidence of new onset of diabetes mellitus and decreased insulin resistance in patients with type 2 DM higher than that of atorvastatin + rosuvastatin (90,91). In an in vitro study, it was found that pitavastatin-treated pancreatic islet β-cells had a lower reduction rate of insulin secretion than those treated with atorvastatin or rosuvastatin. Additionally, the cell survival was better than those of other statins (94). Pitavastatin 1,2, or 4 mg/day was administered for five years to 6,580 individuals with hypercholesterolemia. It has been shown that pitavastatin dramatically lowers HbA1c in diabetic patients (40). Moreover, pitavastatin has been shown to have little effect on coenzyme Q10 in comparison with other statins that caused more reduction in coenzyme Q10 levels, which in turn impacts insulin secretion and glucose metabolism (95). Furthermore, pitavastatin medication increased the rate of glucose uptake by human skeletal muscle more than atorvastatin, pravastatin, or rosuvastatin (96).

3.8. Fluvastatin and glucose homeostasis

Fluvastatin, which was one of the first manufactured but the least effective statins, is most the frequently prescribed statins worldwide in the treatment of hypercholesterolemia. In addition to lowering total and LDL cholesterol, fluvastatin is given to avoid adverse cardiovascular dysfunction (97). For long-term use, the fluvastatin dose is either 20 or 40 mg/day while 80 milligrams per day is the maximum tolerated dose to reduce blood LDL cholesterol levels. Compared to other statins, fluvastatin has a higher tendency to be dissolved in water and increases the risk of rhabdomyolysis as a most significant adverse effect (98).
A study showed that the presence of diabetes increased the risk for cardiovascular complications after a first successful percutaneous coronary intervention by almost 2-fold more than those patients receiving a placebo (99). There was an increased risk for incident diabetes with atorvastatin, rosuvastatin, and simvastatin in a Canadian population-based retrospective cohort study that included more than 1.5 million people. On the other hand, people who were given fluvastatin did not experience a significantly elevated risk. Additionally, this study discovered a connection between the development of diabetes and the strength and dose of statins utilized. A high dose of statin has been linked to a lower risk of cardiovascular disease (CVD) but an increased chance of diabetes than low or moderate dosages (40). A meta-analysis of 32,752 individuals from five extensive clinical trials looked at the effect of statin therapy on the incidence of diabetes in 2011. The probability of acquiring new-onset diabetes was 12% greater for patients receiving intensive statin medication compared to moderate-dose statin therapy (100). Even though fluvastatin has a positive impact on cholesterol levels, it does not increase insulin sensitivity or plasma adiponectin (101).

3.9. Lovastatin and Glucose Homeostasis

Lovastatin is the first discovered cholesterol-lowering statin which was initially isolated from a strain of Aspergillus terreus (102). A population-based retrospective analysis was carried out by Carter et al. (2013) with the participation of 471 250 individuals who were treated with statins and were at least 66 years old before the study. Fluvastatin or lovastatin was administered to 11,923 patients. Atorvastatin, rosuvastatin, and simvastatin contributed to an increase in the risk of diabetes whereas fluvastatin and lovastatin did not raise the risk of type 2 diabetes (103). This finding is supported by another research which included 379,865 non-diabetic individuals and found that lovastatin did not raise fasting glucose (13). Another study conducted on obese mice found that lovastatin can improve insulin sensitivity without affecting insulin levels (104). Moreover, it has been demonstrated by Sharkawi and coauthors that increased antioxidant and anti-inflammatory capacities of administration of both lovastatin and antidiabetic drugs (gliclazide and metformin) could lead to a combined hepatoprotective effect on streptozocin-treated diabetic rats (105).

4. Conclusion

Although statins have a crucial impact on ameliorating cardiovascular disease they have complex effects on glucose homeostasis. Different mechanisms of action are responsible for this pleiotropic effect such as GLUT4 down-regulation, decrease of LDLR expression, reduction of Ca^{2+}-dependent insulin secretion, and inhibition of isoprenoids, geranylgeranyl pyrophosphate (GGPP), farnesyl pyrophosphate (FPP), and CoQ10. Some statins have a negative impact on the glycemic index such as ator- rosu- and simvastatin while other statins have ameliorating effects such as pravastatin. It is highly recommended to further understand these mechanisms and reduce the risk of statins-induced diabetes.

5. References

1. Blais JE, Wei Y, Yap KK, Alwafi H, Ma TT, Brauer R, Lau WC, Man KK, Siu CW, Tan KC, Wong IC, Wei L, Chan EW. Trends in lipid-modifying agent use in 83 countries. Atherosclerosis 2021;328:44-51.
2. Armitage J. The safety of statins in clinical practice. Lancet 2007;370(9601):1781-1790.
3. Althanoon Z, Faisal IM, Ahmad AA, Merkhan MM. Pharmacological aspects of statins are relevant to their structural and physicochemical properties. Systematic Reviews in Pharmacy 2020;11(7):167-171.
4. Stancu C, Sima A. Statins: Mechanism of action and effects. Journal of Cellular and Molecular Medicine 2001;5(4):378-387.
5. Goldstein JL, Brown MS. Regulation of low-density lipoprotein receptors: Implications for pathogenesis and therapy of hypercholesterolemia and atherosclerosis. Circulation 1987;76(3):504-507.
6. Ermakova V, Bataev H, Semenenko N. Comparative benefits of statins in coronary heart disease. Journal of Pharmaceutical Negative Results 2021;12(1):7-13.
7. Alvarez-Jimenez L, Moreno-Cabañas A, Ramirez-Jimenez M, Morales-Palomo F, Ortega JF, Mora-Rodriguez R. Effects of statins and exercise on postprandial lipoproteins in metabolic syndrome vs metabolically healthy individuals. British Journal of Clinical Pharmacology 2021;87(3):955-964.
8. Climent E, Benaiges D, Pedro-Botet J. Hydrophilic or Lipophilic Statins? Frontiers in Cardiovascular Medicine 2021;8.
9. Zhang Q, Dong J, Yu Z. Pleiotropic use of statins as non-lipid-lowering drugs. International Journal of Biological Sciences 2020;16(14):2704-2711.
10. Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. Circulation Research 2017;120(1):229-243.
11. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. Journal of the American College of Cardiology 2016;67(20):2395-2410.
12. Ramkumar S, Raghunath A, Raghunath S. Statin therapy: Review of safety and potential side effects. Acta Cardiologica Sinica 2016;32(6):631-639.
13. Kim J, Lee HS, Lee KY. Effect of statins on fasting glucose in non-diabetic individuals: Nationwide population-based health examination in Korea. Cardiovascular Diabetology 2018;17(1).
14. Millán Núñez-Cortés J, Cases Amenós A, Ascaso Gimilio JF, Barrios Alonso V, Pascual Fuster V, Pedro-Botet Montoya JC, Pintó Sala X, Serrano Cumplido A. Consensus on the Statin of Choice in Patients with Impaired Glucose Metabolism: Results of the DIANA Study. American Journal of Cardiovascular Drugs 2017;17(2):135-142.
15. Okyay K. Pleiotropic effects of statins: New evidences. Turk Kardiyoloji Dernegi Arsivi 2021;49(7):533-535.
16. Liao JK, Laufs U. Pleiotropic effects of statins. Annual Review of Pharmacology and Toxicology 2005;45:89-118.
17. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis 2009;203(2):325-330.
18. Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Faergeman G, Pyörälä K, Miettinen T, Wilhelmsen L, Olsson AG, Wedel H. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. Atherosclerosis Supplements 2004;5(3):81-87.
19. Vidt DG, Cressman MD, Harris S, Pears JS, Hutchinson HG. Rosuvastatin-induced arrest in progression of renal disease. Cardiology 2004;102(1):52-60.
20. Fauchier L, Clementy N, Babuty D. Statin therapy and atrial fibrillation: Systematic review and updated meta-analysis of published randomized controlled trials. Current Opinion in Cardiology 2013;28(1):7-18.
21. Pedersen TR, Kjekshus J, Pyörälä K, Olsson AG, Cook TJ, Musliner TA, Tobert JA, Haghfelt T. Effect of Simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). American Journal of Cardiology 1998;81(3):333-335.
22. Yu W, Zha W, Guo S, Cheng H, Wu J, Liu C. Flos puerariae extract prevents myocardial apoptosis via attenuation oxidative stress in streptozotocin-induced diabetic mice. PLoS ONE 2014;9(5).
23. Zhu ML, Gao ZT, Lu JX, Wang Y, Wang G, Zhu TT, Li P, Liu C, Wang SX, Yang L. Amorphous nano-selenium quantum dots prevent pulmonary arterial hypertension through recoupling endothelial nitric oxide synthase. Aging 2021;13(3):3368-3381.
24. Li P, Yin YL, Guo T, Sun XY, Ma H, Zhu ML, Zhao FR, Xu P, Chen Y, Wan GR, Jiang F, Peng QS, Liu C, Liu LY, Wang SX. Inhibition of Aberrant MicroRNA-133a Expression in Endothelial Cells by Statin Prevents Endothelial Dysfunction by Targeting GTP Cyclohydrolase 1 in Vivo. Circulation 2016;134(22):1752-1765.

25. Park JJ, Yoon M, Cho HW, Cho HJ, Kim KH, Yang DH, Yoo BS, Kang SM, Baek SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH, Choi DJ. C-reactive protein and statins in heart failure with reduced and preserved ejection fraction. Frontiers in Cardiovascular Medicine 2022;9.
26. Wang CY, Liao JK. Current advances in statin treatment: From molecular mechanisms to clinical practice. Archives of Medical Science 2007;3(4 SUPPL. A).
27. Wilmink HW, Twickler MB, Banga JD, Dallinga-Thie GM, Eeltink H, Erkelens DW, Rabelink TJ, Stroes ES. Effect of statin versus fibrate on postprandial endothelial dysfunction: Role of remnant-like particles. Cardiovascular Research 2001;50(3):577-582.
28. Khatiwada N, Hong Z. Potential Benefits and Risks Associated with the Use of Statins. Pharmaceutics 2024;16(2).
29. Crisostomo LML, Souza CAM, Mendes CMC, Coimbra SR, Favarato D, Da Luz PL. Vascular and metabolic response to statin in the mildly hypertensive hypercholesterolemic elderly. Clinics 2008;63(5):589-594.
30. Silva GA, Souza CL, Oliveira M V. Oral glucose tolerance test: Unnecessary requests and suitable conditions for the test. Jornal Brasileiro de Patologia e Medicina Laboratorial 2020;56.
31. AlDabal L. Metabolic, Endocrine, and Immune Consequences of Sleep Deprivation. The Open Respiratory Medicine Journal 2011;5(1):31-43.
32. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of type 2 diabetes mellitus. International Journal of Molecular Sciences 2020;21(17):1-34.
33. Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. Journal of diabetes 2017;9(4):320-324.
34. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. Sleep Medicine Reviews 2007;11(3):163-178.
35. SBPC. Norma PALC.2021. Sociedade Brasileira de Patologia Clínica / Medicina Laboratorial (SBPC/ML) Published online 2021.
36. Araújo LR, Yafi M, Guimarães FPDM, Takayanagui AMM, Lucena JBDS, Golbert A, Campos MA a., Saúde M da, Sartorelli DS, Franco LJ, Prevenção E, Marcondes J a. M. Sociedade Brasileira de Diabetes. Vol 5.; 2020.
37. Choudhury AA, Devi Rajeswari V. Gestational diabetes mellitus - A metabolic and reproductive disorder. Biomedicine and Pharmacotherapy 2021;143.
38. Sunjaya AP, Sunjaya AF, Halim S, Ferdinal F. Risk and Benefits of Statins in Glucose Control Management of Type II Diabetes. International Journal of Angiology 2018;27(3):121-131.
39. Perego C, Da Dalt L, Pirillo A, Galli A, Catapano AL, Norata GD. Cholesterol metabolism, pancreatic β-cell function and diabetes. Biochimica et Biophysica Acta - Molecular Basis of Disease 2019;1865(9):2149-2156.
40. O'Keefe JH, Dinicolantonio JJ, Lavie CJ, Bell DSH. The Influence of statins on glucose tolerance and incipient diabetes. US Endocrinology 2014;10(1):68-74.
41. Cosme P, Rodríguez AB, Garrido M, Espino J. Coping with Oxidative Stress in Reproductive Pathophysiology and Assisted Reproduction: Melatonin as an Emerging Therapeutical Tool. Antioxidants 2023;12(1).
42. Sasaki J, Iwashita M, Kono S. Statins: Beneficial or adverse for glucose metabolism. Journal of Atherosclerosis and Thrombosis 2006;13(3):123-129.
43. S. Kostapanos M, L. Liamis G, J. Milionis H, S. Elisaf M. Do Statins Beneficially or Adversely Affect Glucose Homeostasis? Current Vascular Pharmacology 2010;8(5):612-631.
44. Hammo AA, Althanoon ZA, Ahmad AA. The Protective Effect of Coenzyme Q10 against Doxorubicin-induced Nephrotoxicity in Albino Rats. Revista Electronica de Veterinaria 2022;23(3):314-325.
45. Ali A, Khalaf M, Ahmad AA. A Comprehensive View on Drugs-Induced Cardiotoxicity and Its Prevention. Iraqi Journal of Pharmacy 2024;0(0):0-0.
46. Deichmann R, Lavie C, Andrews S. Coenzyme Q10 and statin-induced mitochondrial dysfunction. Ochsner Journal 2010;10(1):16-21.
47. Brault M, Ray J, Gomez YH, Mantzoros CS, Daskalopoulou SS. Statin treatment and new-onset diabetes: A review of proposed mechanisms. Metabolism: Clinical and Experimental 2014;63(6):735-745.
48. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. Journal of Clinical Investigation 2016;126(1):12-22.
49. Sattar N, Taskinen MR. Statins are diabetogenic - Myth or reality? Atherosclerosis Supplements 2012;13(1):1-10.
50. Vikman J, Jimenez- Feltström J, Nyman P, Eliasson L. Insulin secretion is highly sensitive to desorption of plasma membrane cholesterol. The FASEB Journal 2009;23(1):58-67.
51. Salunkhe VA, Mollet IG, Ofori JK, Malm HA, Esguerra JLS, Reinbothe TM, Stenkula KG, Wendt A, Eliasson L, Vikman J. Dual Effect of Rosuvastatin on Glucose Homeostasis Through Improved Insulin Sensitivity and Reduced Insulin Secretion. EBioMedicine 2016;10:185-194.
52. Cederberg H, Stančáková 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.
53. Navarese EP, Buffon A, Andreotti F, Kozinski M, Welton N, Fabiszak T, Caputo S, Grzesk G, Kubica A, Swiatkiewicz I, Sukiennik A, Kelm M, De Servi S, Kubica J. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. American Journal of Cardiology 2013;111(8):1123-1130.

54. Waters DD, Ho JE, DeMicco DA, Breazna A, Arsenault BJ, Wun CC, Kastelein JJ, Colhoun H, Barter P. Predictors of new-onset diabetes in patients treated with atorvastatin: Results from 3 large randomized clinical trials. Journal of the American College of Cardiology 2011;57(14):1535-1545.
55. Watts GF, Barrett PHR, Ji J, Serone AP, Chan DC, Croft KD, Loehrer F, Johnson AG. Differential regulation of lipoprotein kinetics by atorvastatin and fenofibrate in subjects with the metabolic syndrome. Diabetes 2003;52(3):803-811.
56. Jaam M, Al-Naimi HN, Haddad MM, Abushanab D, Al-Badriyeh D. Comparative efficacy and safety among high-intensity statins. Systematic Review and Meta-Analysis. Journal of Comparative Effectiveness Research 2023;12(3).
57. Cui JY, Zhou RR, Han S, Wang TS, Wang LQ, Xie XH. Statin therapy on glycemic control in type 2 diabetic patients: A network meta-analysis. Journal of Clinical Pharmacy and Therapeutics 2018;43(4):556-570.
58. Sukhija R, Prayaga S, Marashdeh M, Bursac Z, Kakar P, Bansal D, Sachdeva R, Kesan SH, Mehta JL. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. Journal of Investigative Medicine 2009;57(3):495-499.
59. Sattar N, Preiss D, Murray HM. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. Revista Portuguesa de Cardiologia 2010;29(6):1077-1078.
60. Bernardi A, Rocha VZ, Faria-Neto JR. Use of statins and the incidence of type 2 diabetes mellitus. Revista da Associacao Medica Brasileira Published online 2015.
61. Luvai A, Mbagaya W, Hall AS, Barth JH. Rosuvastatin: A review of the pharmacology and clinical effectiveness in cardiovascular disease. Clinical Medicine Insights: Cardiology 2012;6:17-33.
62. Warwick M., Dane A., Raza A, Schneck D. Single- and multiple-dose pharmacokinetics and safety of the new HMG-CoA reductase inhibitor ZD4522. Atherosclerosis 2000;151(1):39.
63. Martin PD, Mitchell PD, Schneck DW. Pharmacodynamic effects and pharmacokinetics of a new HMG-CoA reductase inhibitor, rosuvastatin, after morning or evening administration in healthy volunteers. British Journal of Clinical Pharmacology 2002;54(5):472-477.
64. Abbasi F, Lamendola C, Harris CS, Harris V, Tsai MS, Tripathi P, Abbas F, Reaven GM, Reaven PD, Snyder MP, Kim SH, Knowles JW. Statins Are Associated With Increased Insulin Resistance and Secretion. Arteriosclerosis, Thrombosis, and Vascular Biology 2021;41(11):2786-2797.
65. Bellia A, Rizza S, Lombardo MF, Donadel G, Fabiano R, Andreadi K, Quon MJ, Sbraccia P, Federici M, Tesauro M, Cardillo C, Lauro D. Deterioration of glucose homeostasis in type 2 diabetic patients one year after beginning of statins therapy. Atherosclerosis 2012;223(1):197-203.
66. Alvarez-Jimenez L, Morales-Palomo F, Moreno-Cabañas A, Ortega JF, Mora-Rodríguez R. Effects of statin therapy on glycemic control and insulin resistance: A systematic review and meta-analysis. European Journal of Pharmacology 2023;947.
67. Packard CJ, Boren J, Taskinen MR. Causes and Consequences of Hypertriglyceridemia. Frontiers in Endocrinology 2020;11.
68. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metabolism 2013;17(2):162-184.
69. Watson RT, Pessin JE. Bridging the GAP between insulin signaling and GLUT4 translocation. Trends in Biochemical Sciences 2006;31(4):215-222.
70. Karam JG, Loney-Hutchinson L, McFarlane SI. High-dose atorvastatin after stroke or transient ischemic attack: The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. Journal of the cardiometabolic syndrome 2008;3(1):68-69.
71. Parida S, Swain TR, Routray SN, Maiti R. Effect of atorvastatin on glycaemic parameters in normoglycaemic and prediabetic subjects: A prospective, panel study. Journal of Clinical and Diagnostic Research 2017;11(2):FC04-FC09.
72. Thongtang N, Tangkittikasem N, Samaithongcharoen K, Piyapromdee J, Srinonprasert V, Sriussadaporn S. Effect of switching from low-dose simvastatin to high-dose atorvastatin on glucose homeostasis and cognitive function in type 2 diabetes. Vascular Health and Risk Management 2020;16:367-377.
73. Yu Q, Wang F, Meng X, Gong Y, Wang Y, Xu C, Wang S. Short-term use of atorvastatin affects glucose homeostasis and suppresses the expression of LDL receptors in the pancreas of mice. Molecular Medicine Reports 2018;18(3):2780-2788.
74. Cheng D, Wang Y, Gao S, Wang X, Sun W, Bai L, Cheng G, Chu Y, Zhao S, Liu E. Atorvastatin delays the glucose clearance rate in hypercholesterolemic rabbits. Biomedicine and Pharmacotherapy 2015;72:24-29.
75. Ferri N, Ruscica M, Fazio S, Corsini A. Low-Density Lipoprotein Cholesterol-Lowering Drugs: A Narrative Review. Journal of Clinical Medicine 2024;13(4).
76. Subhan M, Faryal R, Macreadie I. Exploitation of Aspergillus terreus for the production of natural statins. Journal of Fungi 2016;2(2).
77. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: A double-blind randomised trial. The Lancet 2010;376(9753):1658-1669.
78. Chamberlain LH. Inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes. FEBS Letters 2001;507(3):357-361.
79. Yada T, Nakata M, Shiraishi T, Kakei M. Inhibition by simvastatin, but not pravastatin, of glucose-induced cytosolic Ca2+ signalling and insulin secretion due to blockade of L-type Ca2+ channels in rat islet β-cells. British Journal of Pharmacology 1999;126(5):1205-1213.

80. Razali NR, Huri HZ, Ibrahim L, Vethakkan SR, Abdullah BM. Glycemic effects of simvastatin: Where do we stand? Brazilian Journal of Pharmaceutical Sciences 2018;54(1).
81. Scattolini V, Luni C, Zambon A, Galvanin S, Gagliano O, Ciubotaru CD, Avogaro A, Mammano F, Elvassore N, Fadini GP. Simvastatin Rapidly and Reversibly Inhibits Insulin Secretion in Intact Single-Islet Cultures. Diabetes Therapy 2016;7(4):679-693.
82. Paolisso G, Barbagallo M, Petrella G, Ragno E, Barbieri M, Giordano M, Varricchio M. Effects of simvastatin and atorvastatin administration on insulin resistance and respiratory quotient in aged dyslipidemic non-insulin dependent diabetic patients. Atherosclerosis 2000;150(1):121-127.
83. Panajatovic MV, Singh F, Krähenbühl S, Bouitbir J. Simvastatin impairs glucose homeostasis in mice depending on PGC-1α skeletal muscle expression. Biomedicines 2020;8(9).
84. Teachey D, Sheen C, Seif AE, Brown VI, Grupp SA. Targeting HMG-CoA Reductase in Acute Lymphoblastic Leukemia (ALL): Statins Inhibit Proliferation and Induce Apoptosis in ALL Cells. Blood 2008;112(11):2927-2927.
85. Sugiyama S, Fukushima H, Kugiyama K, Maruyoshi H, Kojima S, Funahashi T, Sakamoto T, Horibata Y, Watanabe K, Koga H, Sugamura K, Otsuka F, Shimomura I, Ogawa H. Pravastatin improved glucose metabolism associated with increasing plasma adiponectin in patients with impaired glucose tolerance and coronary artery disease. Atherosclerosis 2007;194(2).
86. Otani M, Yamamoto M, Harada M, Otsuki M. Effect of long- and short-term treatments with pravastatin on diabetes mellitus and pancreatic fibrosis in the Otsuka-Long-Evans-Tokushima Fatty rat. British Journal of Pharmacology 2010;159(2):462-473.
87. Yu Y, Ohmori K, Chen Y, Sato C, Kiyomoto H, Shinomiya K, Takeuchi H, Mizushige K, Kohno M. Effects of pravastatin on progression of glucose intolerance and cardiovascular remodeling in a type II diabetes model. Journal of the American College of Cardiology 2004;44(4):904-913.
88. Kaya HK, Demirtas B, Yokus B, Kesim DA, Tasdemir E, Sermet A. Comparative effects of pravastatin and rosuvastatin on carbohydrate metabolism in an experimental diabetic rat model. Acta Pharmaceutica 2024;74(1):117-130.
89. Chan P, Shao L, Tomlinson B, Zhang Y, Liu ZM. An evaluation of pitavastatin for the treatment of hypercholesterolemia. Expert Opinion on Pharmacotherapy 2019;20(1):103-113.
90. Frampton JE. Inclisiran: A Review in Hypercholesterolemia. American Journal of Cardiovascular Drugs 2023;23(2):219-230.
91. Benekos T, Kosmeri C, Vlahos A, Milionis H. Nine-year overview of dyslipidemia management in children with heterozygous familial hypercholesterolemia: A university hospital outpatient lipid clinic project in Northwestern Greece. Journal of Pediatric Endocrinology and Metabolism 2020;33(4):533-538.
92. Seo WW, Seo SI, Kim Y, Yoo JJ, Shin WG, Kim J, You SC, Park RW, Park YM, Kim KJ, Rhee SY, Park M, Jin ES, Kim SE. Impact of pitavastatin on new-onset diabetes mellitus compared to atorvastatin and rosuvastatin: a distributed network analysis of 10 real-world databases. Cardiovascular Diabetology 2022;21(1).
93. Abbas S, Khan MN, Samor NA, Abbas H, Khan RP, Kamran J. To Compare the Effects of Pitavastatin on Insulin Resistance in Patients With Type 2 Diabetes Mellitus With Hypercholesterolemia Who Were Previously Being Treated With Atorvastatin. Pakistan Armed Forces Medical Journal 2019;69:S393-S398.
94. Hussain A, Kaler J, Ray SD. The Benefits Outweigh the Risks of Treating Hypercholesterolemia: The Statin Dilemma. Cureus Published online 2023.
95. Koh KK, Lim S, Sakuma I, Quon MJ. Caveats to aggressive lowering of lipids by specific statins. International Journal of Cardiology 2012;154(2):97-101.
96. Zhao W, Zhao SP. Different effects of statins on induction of diabetes mellitus: An experimental study. Drug Design, Development and Therapy 2015;9:6211-6223.
97. Adams SP, Sekhon SS, Wright JM, Tsang M. Fluvastatin for lowering lipids. Cochrane Database of Systematic Reviews 2016;2016(7).
98. Sorathia K, Lumbhani A, Chauhan S, Patel M, Soni T, Suhagia BN. Development and Optimization of Fluvastatin Sodium Loaded Biodegradable Microspheres. International Journal of Pharmaceutical Sciences and Drug Research Published online 2023:407-415.
99. Arampatzis CA, Goedhart D, Serruys PW, Saia F, Lemos PA, De Feyter P. Fluvastatin reduces the impact of diabetes on long-term outcome after coronary intervention - A Lescol Intervention Prevention Study (LIPS) substudy. American Heart Journal 2005;149(2):329-335.
100. Preiss D, SRK S, Welsh P, Sattar N, Ray K. Risk of incident diabetes on intensive compared to moderate dose statin therapy: a collaborative meta-analysis of randomized trials. Diabetes 2011;60(SUPPL. 1):A88.
101. Sonmez A, Dogru T, Tasci I, Yilmaz MI, Pinar M, Naharci I, Bingol N, Kilic S, Demirtas A, Bingol S, Ozgurtas T, Erikci S. The effect of fluvastatin on plasma adiponectin levels in dyslipidaemia. Clinical Endocrinology 2006;64(5):567-572.
102. Hassan A, Saleem Y, Chaudhry MN, Asghar A, Saleem M, Nawaz S, Syed Q, Iqbal MS, Shahzad K. Optimization of process variables for increased production of lovastatin in Aspergillus terreus PU-PCSIR1 and its characterization. Pakistan journal of pharmaceutical sciences 2019;32(1):363-370.
103. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: Population based study. BMJ (Online) 2013;346(7911).

104. Li J, Ding L, Song B, Xiao X, Qi M, Yang Q, Yang Q, Tang X, Wang Z, Yang L. Emodin improves lipid and glucose metabolism in high fat diet-induced obese mice through regulating SREBP pathway. European Journal of Pharmacology 2016;770:99-109.

105. Sharkawi SMZ, El-Shoura EAM, Abo-Youssef AM, Hemeida RAM. The potential hepatoprotective effects of lovastatin combined with oral hypoglycemic agents in streptozotocin-induced diabetes in rats. Immunopharmacology and Immunotoxicology 2020;42(2):165-173.

مناهج شاملة لتأثير الستاتينات على توازن الجلوكوز

الخلاصة

المقدمة: يُعد اضطراب تحمل الجلوكوز عامل خطر رئيسي لأمراض القلب والأوعية الدموية. تُوصف الستاتينات عادةً لخفض مستويات الكوليسترول، إلا أن آثارها المحتملة على تحمل الجلوكوز والتسبب في الإصابة بمرض السكري من النوع الثاني قد لفتت الانتباه. **الهدف:** تُسلط هذه المراجعة الضوء على العلاقة بين أدوية الستاتينات وتوازن الجلوكوز. **المنهجية:** أُجري بحث موسع في الأدبيات العلمية على قواعد بيانات إلكترونية مختلفة مثل PubMed و Scopusو Web of Scienceو .Science Direct **الاستنتاج:** طُرحت آليات مختلفة، وقد تكون مسؤولة عن هذا التأثير متعدد التأثيرات للستاتينات على توازن الجلوكوز. وقد أشارت العديد من التجارب السريرية والتحليلات التلوية إلى جدل كبير حول تحمل/عدم تحمل الجلوكوز الناتج عن الستاتينات، وذلك بناءً على نوع الستاتين وجرعته. وهذا يحث الباحثين على إجراء المزيد من الدراسات لتوضيح هذا التأثير متعدد التأثيرات لكل ستاتين. على الرغم من تحسن المعرفة الحالية فيما يتعلق بتأثير الستاتينات على المؤشر الجلوكوزي، إلا أن العديد من الجوانب الجزيئية/الخلوية لم يتم تحديدها بعد.

الكلمات المفتاحية : مرض السكري؛ توازن الجلوكوز؛ مقاومة الأنسولين؛ الستاتينات.