Signaling Pathways Behind the Effect of Atorvastatin in Glucose Homeostasis

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ABSTRACT

Background: cardiovascular diseases (CVD) are significantly increased by dyslipidemia, while statins, especially atorvastatin, efficiently lower low-density lipoprotein (LDL) cholesterol levels, and decrease the risk of cardiovascular diseases. However, there are raising concern about the potential role of statins in inducing diabetes.

Aim: to highlight the impact of atorvastatin on glucose homeostasis, focusing on the mechanisms through which atorvastatin influences glucose metabolism.

Method: An extensive literature search has been conducted on various electronic databases such as PubMed, Scopus, Web of Science, and Science Direct. The review reported the effect of atorvastatin on main organs that are related to glucose homeostasis such as liver, adipose tissue and skeletal muscle. The mechanisms that underlie the atorvastatin-induced glucose intolerance effects include decreased insulin signaling in both muscle and adipose tissues, increased hepatic gluconeogenesis, and suppression of the mevalonate pathway.

Conclusions: The present knowledge regarding the impact of atorvastatin on glucose metabolism has been improved but several molecular/cellular signaling pathways are yet to be determined.

Keywords: Atorvastatin, Diabetes, Free fatty acids, Insulin resistance, Mevalonate pathway.

مسارات الإشارة وراء تأثير الأتورفاستاتين في توازن الجلوكوز

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الخلاصة

الخلفية: تزداد أمراض القلب والأوعية الدموية بشكل كبير بسبب خلل شحميات الدم، في حين تعمل الستاتينات، وخاصة أتورفاستاتين، على خفض مستويات الكوليسترول منخفض الكثافة (LDL) بكفاءة، وتقليل خطر الإصابة بأمراض القلب والأوعية الدموية. ومع ذلك، هناك مخاوف متزايدة بشأن الدور المحتمل للستاتينات في إحداث مرض السكري.

الهدف: تسليط الضوء على تأثير أتورفاستاتين على توازن الجلوكوز، مع التركيز على الآليات التي يؤثر بها أتورفاستاتين على عملية التمثيل الغذائي للجلوكوز.

الطريقة: تم إجراء بحث موسع في الأدبيات على قواعد بيانات إلكترونية مختلفة مثل PubMed وScopus وWeb of Science وScience Direct. أفاد الاستعراض بتأثير أتورفاستاتين على الأعضاء الرئيسية المرتبطة بتوازن الجلوكوز مثل الكبد والأنسجة الدهنية والعضلات الهيكلية. تشمل الآليات التي تكمن وراء تأثيرات عدم تحمل الجلوكوز الناجمة عن أتورفاستاتين انخفاض إشارات الأنسولين في كل من الأنسجة العضلية والدهنية، وزيادة تكوين الجلوكوز في الكبد، وقمع مسار ميفالونات.

الاستنتاجات: لقد تم تحسين المعرفة الحالية فيما يتعلق بتأثير أتورفاستاتين على عملية التمثيل الغذائي للجلوكوز ولكن العديد من مسارات الإشارات الجزيئية / الخلوية لم يتم تحديدها بعد.

الكلمات المفتاحية: أتورفاستاتين، داء السكري، الأحماض الدهنية الحرة، مقاومة الأنسولين، مسار ميفالونات.

INTRODUCTION

Dyslipidemia is an important risk factor for cardiovascular diseases [1]. Statins have been referred to as an effective treatment for high plasma cholesterol level by reducing low-density lipoprotein (LDL) cholesterol levels through 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition. Numerous prospective studies have demonstrated the cardioprotective properties of statins. The advantageous impact of statins on both primary and secondary prevention of cardiovascular events occurs through reducing LDL-cholesterol levels [2].

Recent studies reported that statins have different cholesterol-independent 'pleiotropic' effects[3,4,5]. Despite the established effectiveness in treating and preventing CVD, some physicians have become hesitant to prescribe statins in the past decade, particularly for those at risk of developing diabetes. The rationale for this prescription issue is based on a frequently referenced meta-analysis indicating a 9% rise in diabetes incidence among statin users[6]. This meta-analysis study includes a robust (n = 17,603 subjects) 5-year follow-up randomized trial demonstrating correlations between elevated levels of glycated hemoglobin (HbA1c) as an indicator of type 2 diabetes mellitus (T2DM) and statins use [7].

Concerning physiochemical features, statins can be categorized into lipophilic statins such as atorvastatin, simvastatin, and lovastatin, and hydrophilic statins like pravastatin and rosuvastatin [8]. Generally, lipophilic statins are more prone to induce diabetes compared to their hydrophilic counterparts, potentially due to their capacity to infiltrate extrahepatic tissues such as the pancreas, muscle, and adipose tissue. In contrast, hydrophilic statins are preferentially accumulated by the liver, exhibiting limited distribution to extrahepatic tissues, hence demonstrating hepato-selectivity; consequently, they exert less disruption on cholesterol metabolism in extrahepatic tissues, resulting in a reduced diabetogenic effect with prolonged usage [9].

On the other hand, lipophilic statins with enhanced penetration into the cellular membrane, directly influence membrane channels such as KATP channels and voltage-gated Ca^{2+} channels. Furthermore, lipophilic statins influence insulin production or secretion [9]. Atorvastatin is a lipophilic statin that is commonly prescribed to treat hypercholesterolemia and prevent coronary artery diseases. However, there is a controversy about its effect on glucose tolerance state.

Wang and colleagues concluded that mice with hyperlipidemia showed decreased fasting blood glucose levels when using atorvastatin treatment for three weeks [10]. While a present study hypothesized that atorvastatin treatment for 16 weeks did not affect glucose metabolism in rabbits [11].

The aim of the present review is to highlight the impact of atorvastatin on the glucose homeostasis with the most important suggested mechanisms.

Methodology

We searched scholarly literature up to December 2024 from the PubMed.gov (National Institutes of Health, National Library of Medicine), EMBASE, Scopus, Web of Science, and Science Direct databases. The examination of databases for studies encompassed the terms "statin", "atorvastatin", "HOMA-IR", " glucose homeostasis model insulin resistance", "glycated hemoglobin", "HbA1c" and/or "AKT" within the title or abstract. The review included researches conducted on humans, namely adults,and animals, which published in English. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [12]. Furthermore, we omitted studies involving individuals with organ transplants, or renal disease, as these disorders influence glycemic management.

Impact of Atorvastatin on Glucose Homeostasis

Patients with hypercholesterolemia and patients with hypertriglyceridemia have been reported to benefit from atorvastatin in dose-dependant decline of total cholesterol, (LDL)-cholesterol, and triglyceride levels [13].

As a lipophilic statin, atorvastatin has been shown to have adverse effects on glucose metabolism, especially in people who have diabetes or glucose intolerance [14]. Cederberg et al., (2015) reported that there is a dose-dependent activation of insulin secretion and insulin resistance during utilizing simvastatin and atorvastatin [15]. Most studies and clinical investigations demonstrated that high-dose atorvastatin increased the incidence of new onset diabetes more than lesser doses [16]. 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, respectively [8].

Also, short-term atorvastatin use impairs glucose tolerance and suppresses the expression of low density lipoprotein receptor (LDLR) in mice's pancreatic islets, suggesting that more research is necessary to address LDLR's role in the diabetogenic action of statins [10]. In contrast, rabbits with normal blood cholesterol levels showed no change in their glucose equilibrium after long-term atorvastatin treatment [11]. More research is required to find the effect of the duration of treatment of atorvastatin on glucose homeostasis. Ethnic differences may influence atorvastatin pharmacodynamics. It decreases the ability of insulin secretion in Japanese people more than their Caucasian counterparts. However, it has a negligible effect on insulin sensitivity but still can have a detrimental effect on the equilibrium of glucose in people with T2DM. This result is based on Yokote K et al.,(2009) findings who found a rise in HbA1c levels in the atorvastatin group, which indicates a decline in glycemic control during the course of the 12-week treatment [17]. However, increases in glucose and HbA1c levels as well as incidence of DM in patients treated by atorvastatin were documented in the PROVE-IT TIMI 22 sub-study[18]. Alvarez-Jimenez et al.,(2021) showed that HBA1c is increased significantly as a result of atorvastatin, with a mean difference of 0.24% when the participants had normal HbA1c readings below 6.5% (5.78± 0.28). While 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%[19]. HOMA-IR index was significantly elevated as a result of the administration of atorvastatin in both people with normal and high HOMA-IR [20].

Additionally, in a large prospective research with 8749 males, It was demonstrated that taking atorvastatin could increase the occurrence of T2DM by 46 percent, which was linked to a 24 percent rise in HOMA-IR and a 12 percent reduction in insulin production [15].In contrast, Tabaei et al., (2022) found that atorvastatin can help individuals with type 2 Diabetes Mellitus (T2DM) lower their HbA1c and insulin resistance levels after three months of treatment compared to the placebo-treated control group. Moreover, the atorvastatin group experienced a drop in fasting blood glucose (FBS) levels but this decrease was not statistically significant [21]. Anther meta-analysis that included 32,752 participants found that high-intensity statins (atorvastatin, rosuvastatin, and simvastatin) were more frequently linked to the incidence of T2DMcomapred to moderately intense statins (pravastatin, pitavastatin)[22]. Abbasi et al., (2021) performed a clinical trial using 40 mg/d of atorvastatin in persons who did not have type 2 diabetes or atherosclerotic cardiovascular disease at baseline. In the graded-glucose infusion test, atorvastatin could elevate insulin secretion by a median of 9% and increase insulin resistance by a median of 8% during the insulin suppression test at 10 weeks compared to baseline. Oral glucose tolerance test and fasting insulin both are slightly increased in the same study[23].

Difference between Hydrophilic and Lipophilic Statin

The lipophilic statin atorvastatin and hydrophilic statin such as rosuvastatin are both widely used statins that lower cholesterol levels. Despite their similar primary function, they differ notably in their lipophilicity and hydrophilicity, which influence their tissue distribution and potential side effects [24].

There are notable distinctions between atorvastatin and rosuvastatin when compared according to their lipophilicity and effects on pancreatic. As a lipophilic statin, atorvastatin readily penetrates cell membranes, leading to broader distribution in various tissues, including non-hepatic cells and those of pancreatic β-cells [25]. This trait which causes increased intracellular accumulation may have more cytotoxic consequences and may reduce insulin sensitivity, as demonstrated by rising fasting blood glucose (FBG) levels and rising HOMA-IR values over time. According to Wei et al., (2016), atorvastatin has been demonstrated to decrease pancreatic fibrosis and increase insulin sensitivity in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, which are prone to insulin resistance and T2DM [26]. On the other hand, rosuvastatin is more hydrophilic and mainly acts in the liver, with little penetration into extrahepatic organs. Its uptake into hepatocytes is primarily mediated by active transport mechanisms, such as the organic anion transporting polypeptide (OATP) [27]. However, another study has explored the association between rosuvastatin use and acute pancreatitis, indicating a need for further research to fully understand its impact on pancreatic health [28]. Finally, the accumulating results highlight how crucial it is to take lipophilicity into account when assessing these statins' safety profiles.

Mechanisms of Atorvastatin on Glucose Homeostasis

The exact mechanisms by which statins cause T2DM remain unclear but it is possible that both on-target and off-target effects have a role. Atorvastatin affects glucose homeostasis by inhibiting the mevalonate pathway[29]. The synthesis of sterol and non-sterol isoprenoids by the highly conserved mevalonate system is a crucial

metabolic mechanism that affects numerous cellular functions (Figure 1)[30].

Sterol isoprenoid cholesterol is a key precursor of lipoproteins, bile acids, and steroid hormones, while non-sterol isoprenoids like ubiquinone (coenzyme Q10), and dolichols are necessary for gene expression, cell growth and differentiation, protein glycosylation, and cytoskeletal assembly. Non-sterol isoprenoids are crucial for the post-translational modification of intracellular signaling proteins[29],[30]. In particular, dolichols facilitate the N-glycosylation of proteins, and their inhibition can hamper the expression of receptors as well as the synthesis of structural proteins [31]. Farnesyl pyrophosphate and geranylgeranyl pyrophosphate, two byproducts of the mevalonate process, also contribute to cell development and maintenance and lower apoptosis [32],[33], and these byproducts are also necessary for post-translational modification of GTPases and lamins, which are crucial for chromatin architecture and cell maintenance, as well as the activation of regulatory GTP-binding proteins. Apoptosis is happened by weak nuclear membranes caused by the dysprenylation of lamin and small GTPases [34]. In addition, electron transport proteins, heme A, and prenylated proteins are additional substances that are impacted by inhibition of the mevalonate pathway. These compounds can have downstream effects such as decreased excitability and stability of cell membranes, compromised signal transduction and intracellular trafficking, and impaired protein structure and function, all of which can result in decreased gene expression and dysfunction or decrease in membrane receptors, transporters, and channels [35].

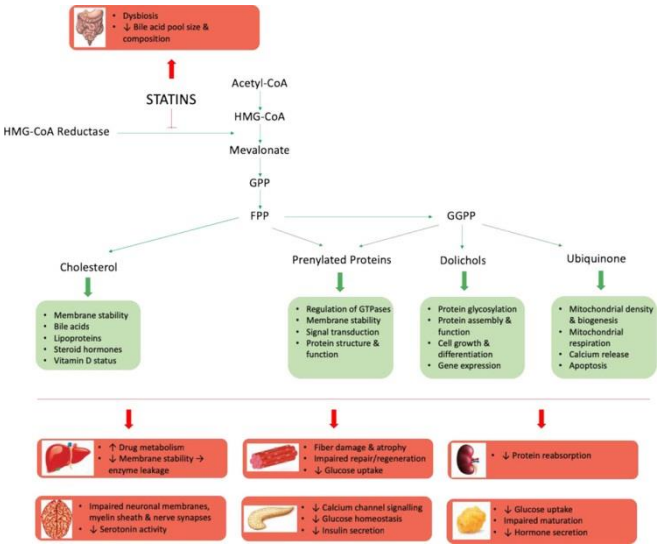

Figure 1: Mevalonate system and its effects on numerous cellular functions (adapted from [36]).

Long-term statin medications raise synthesis of glucose through the upregulation of the gene expression of important enzymes that enhance the liver's gluconeogenesis [37]. Principal enzymes utilized in the synthesis of acetyl-CoA were shown to be upregulated, and hepatocytes were shown to exhibit mild global acetylation of pan-protein and histone H4 (the protein involved in the structure of chromatin in cells) [38]. Furthermore, atorvastatin has been demonstrated to interfere with the insulin signaling pathway and inhibit the GLUT-4 transporter, which is involved in peripheral cells' uptake of glucose [39],[40]. The plasma free fatty acids (FFA), hormones like leptin and adiponectin, β-cell function, damage of β-cell, and adipocyte maturation/differentiation can all be altered by statins[22],[40],[41]. Reduction of insulin secretion has also been linked to other pathways including epigenetic control mediated by certain microRNAs[29]. Figure 2 summarizes the intricate pathophysiologic molecular pathways of statin-induced type 2 diabetes, which are further explained in the next sections.

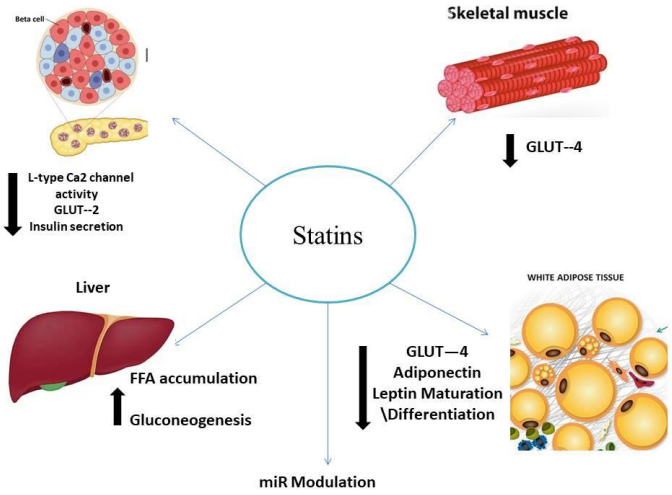

Figure 2: Principal mechanisms for T2DM development induced by statins

Effect of Atorvastatin on Adipocyte

Multi-vital organs are related to the homeostatic regulation of blood glucose such as the liver, adipose tissue, and skeletal muscle [41]. A recent study has shown that several small GTP-binding proteins (G-proteins) in adipocytes are affected by statin treatment such as GLUT-4, Akt (a serine-threonine kinase), insulin receptor (INSR), and caveolae integrity. According to several investigations, atorvastatin impairs glucose tolerance by lowering the expression of GLUT-4 at the cell membrane in adipocytes and in mouse-white adipose tissue [35,37].

By inhibiting isoprenoid production, statins have been shown to reduce GLUT-4 translocation to the plasma membrane [44]. Actually, a number of proteins utilized in the GLUT-4 translocation pathway depend on isoprenylation to operate properly. It has been shown that atorvastatin inhibits the formation of geranylgeranyl pyrophosphate, which in turn affects the plasma membrane co-localization of Rab-4 and RhoA. Atorvastatin could interfere with the insulin signaling pathway via inhibiting isoprenoid-dependent proteins RhoA and Rab-4 which are involved in the insulin-induced translocation of GLUT-4. In addition, atorvastatin could reduce the active membrane fraction of RhoA and Rab4 in adipocytes and, consequently, regulate IRS-1 activity [45].

It is notable that the absence of secretion of insulin-sensitizing hormone due to atorvastatin could impact the process of differentiation of preadipocyte to adipocyte. The underlying mechanism of this effect is probably due to a reduction in the expression of peroxisome proliferator-activated receptor γ (PPARγ) and transcription factors (CCAAT/enhancer-binding protein) [29].

Effect of Atorvastatin on Liver

The liver can be affected by many drugs because it is the main route of metabolism of many exogenous chemical compounds [46]. An increase in fasting blood glucose levels is linked to atorvastatin medication [47]. Statins have been shown to enhance the production of glucose in the body through the activation of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, both of which are considered gluconeogenic enzymes in the hepatocytes [48],[49]. Insulin resistance and T2DM were exacerbated by increased hepatic gluconeogenesis. In the liver, the primary glucose transporter is glucose transporter 2 (GLUT2), while Glucokinase (GCK) is a crucial regulator of glycolysis [48]. Atorvastatin was shown to partially reduce glucose uptake by suppressing the expression of GLUT2 and GCK in the liver [50].

Regarding FFAs, it has been shown that T2DM can be developed as a result of an excessive buildup of FFAs in hepatocytes [51],[52]. Interestingly, atorvastatin and rosuvastatin treatment raises the expression of a small protein called thyroid hormone-responsive spot 14 protein, which is mostly expressed in the hepatocytes. The aforementioned protein is regarded as a regulator of the lipogenic processes by regulating the expression and activity of different lipogenic genes [51],[53],[54].The negative impact of statins in the liver cells are summarized in Figure 3.

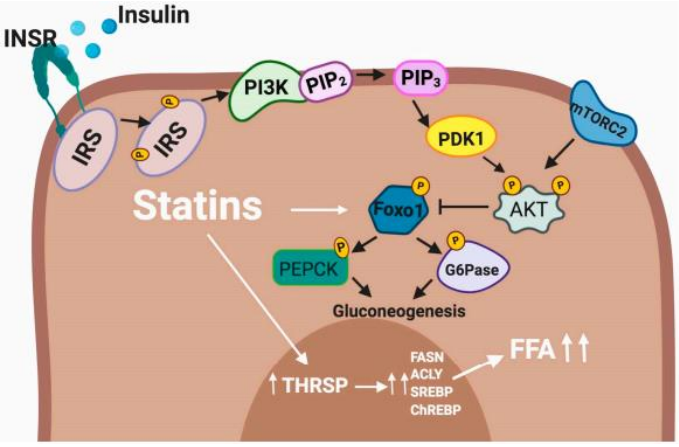

Figure 3: The effect of statins in the hepatocyte (Adapted from [9]).

Effect of Atorvastatin in Skeletal Muscle

Skeletal muscle is the major part that uses glucose which enters the bloodstream, and any disruption in this tissue's ability to metabolite glucose may lead to the development of T2DM [52]. As previously mentioned, when insulin binds to INSR, Akt is activated and vesicles containing GLUT-4 are translocated to the cell membrane in C2C12 myotubes without altering the expression of the whole GLUT-4 protein[51],[55],[56].

Hexokinase II (HXKII) and GLUT4 are the analogs of (GLUT2) which are expressed in skeletal muscle and adipose tissue, respectively[11],[13]. Atorvastatin may lower the amount of the GLUT4 protein in fat cells and inhibit glucose uptake by adipocytes and skeletal muscle leading to a rise in the risk of incident T2DM [53],[55]. In addition, atorvastatin can impair the INSR's intracellular signaling (the Akt/mTOR pathway) which leads to suppression of insulin-stimulated uptake of glucose. Impaired Akt-mediated phosphorylation of GSK3β is most likely the cause of this defective GLUT-4 translocation [57]. Atorvastatin therapy markedly decreased the phosphorylation of Akt Ser473 [58],[59].

CONCLUSIONS

Effects of atorvastatin on glucose homeostasis occur through several mechanisms involving mevalonate pathway inhibition which is necessary for the synthesis of numerous chemical components that impact cellular processes. Atorvastatin affects the function of the liver by upregulating important gluconeogenic enzymes (G6Pase and PEPCK), increasing hepatic glucose production and may be exacerbate insulin resistance. Additionally, it interferes with skeletal muscle's insulin-stimulated glucose uptake,

possibly by impairing Akt/mTOR signaling pathways. Furthermore, atorvastatin affects adipocytes by altering GLUT-4 expression and translocation, reducing insulin signaling in adipose tissue, which in turn affects glucose uptake. Further research is necessary to understand the more molecular signaling pathways using different doses, and durations, and in different pathophysiological conditions.

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Conflict of Interest

There is no conflict of interest.

Highlights

- The use of atorvastatin is associated with a dose-dependent and increased new-onset diabetes.
- Insulin signaling and GLUT-4 translocation are impaired in adipocytes due to the use of atorvastatin.
- In the liver, atorvastatin lowers glucose absorption and increases gluconeogenesis.
- In skeletal muscle: it is reduced glucose absorption and insulin signaling.

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