

A Differential Review of Statins, Their Distinct Differences, and the Underlying Mechanisms of Vasodilation

Running Title: Statins and Vasodilation

Roghayeh Pourbagher¹ , Ali Nosrati Andevary^{2*} , Faegheh Bahri³ , Afsaneh Pourzaman⁴ , Rana Douseh⁵ , Durdi Qujeq^{6,7*} 

¹ Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

² Department of Clinical Biochemistry, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran.

³ Department of Clinical Biochemistry, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran.

⁴ Department of Pharmacology and Toxicology, School of Medicine, Babol University of Medical Sciences, Babol, Iran

⁵ Department of Pharmacology and Toxicology, School of Medicine, Babol University of Medical Sciences, Babol, Iran

⁶ Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

⁷ Department of Clinical Biochemistry, School of Medicine, Babol University of Medical Sciences, Babol, Iran.

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Corresponding authors

*Department of Clinical Biochemistry, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
Tel: +98-9362090578

E-mail: nosrati.ali70@gmail.com

ORCID ID: 0000-0002-8699-4688

** Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

**Department of Clinical Biochemistry, School of Medicine, Babol University of Medical Sciences, Babol, Iran.
Tel: +98- 9111144530

E-mail: d.queq@mubabol.ac.ir ,

dqueq@gmail.com

ORCID ID:

0000-0003-1344-9344

Abstract

Statins exert their effects by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA-R) in the mevalonate pathway. The purpose of this study is to investigate statins, their differences, and the associated mechanisms of vasodilation. Seven statins are used in the clinical setting. These statins include atorvastatin, lovastatin, fluvastatin, simvastatin, pravastatin, pitavastatin, and rosuvastatin. Statins differ in several ways, including their origin, membrane permeability, drug interactions, and affinity for HMG-CoA-R. Fungi-derived statins include lovastatin, pravastatin, and simvastatin.

In contrast, atorvastatin, fluvastatin, pitavastatin, and rosuvastatin are produced by chemical synthesis. Furthermore, lipophilic statins, including atorvastatin, lovastatin, simvastatin, fluvastatin, and pitavastatin, but not rosuvastatin and pravastatin, exhibit hydrophilic properties. Hydrophilic statins experience fewer drug interactions than lipophilic statins. Pitavastatin and pravastatin exhibit lower efficacy in reducing cholesterol levels. In contrast, rosuvastatin and atorvastatin lower cholesterol levels more than other statins. Since lipophilic statins readily enter non-hepatic cells, these statins may improve vasodilation more than hydrophilic statins. The action of statins is due to the inhibition of the production or activity of cholesterol, geranyl-geranyl pyrophosphate (GGPP), RhoA/ROCK, phosphatase and tensin homolog (PTEN), and nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B), and the stimulation of the production or activity of insulin and the PI3K/AKT/eNOS pathway. Considering the more potent inhibitory effect of rosuvastatin on the mevalonate pathway, along with the substantial inhibitory activity of atorvastatin on this pathway and its lipophilic characteristics, these two agents produce a more pronounced vasodilatory effect than other statins.

Keywords: Statin, Vasodilation, Insulin, Cholesterol, GGPP.

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Introduction

Statins were originally derived from fungi. Mevastatin was the initial statin isolated from *Penicillium citrinum*. However, it was never offered to the market. Lovastatin was the first statin derived from fungi to be made available to the public. It is primarily produced by *Aspergillus terreus* strains (1, 2). Cerivastatin was withdrawn from the global market because of renal complications and rhabdomyolysis (3). Seven statins are used in the clinical setting. These statins include atorvastatin, lovastatin, fluvastatin, simvastatin, pravastatin, pitavastatin, and rosuvastatin. Pitavastatin and rosuvastatin are newer than other statins (4, 5). Statins differ in several ways, including their origin, membrane permeability, drug interactions, and affinity for 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA-R), which will be discussed below. In addition to inhibiting cholesterol synthesis, statins participate in vasodilation mechanisms (6). This research aimed to explore statins, including their distinctions and the vasodilation mechanisms associated with them.

The Main Function of Statins in Cells

The liver is the primary site of cholesterol synthesis. It is involved in hypercholesterolemia. The role of the liver in the development of hypercholesterolemia is crucial because cholesterol is a major component of low-density lipoprotein cholesterol (LDL-C), or "bad" cholesterol. However, due to the beneficial functions of cholesterol within the cell, such as its functions in the cell membrane, signaling pathways, and intracellular transport, the production of cholesterol by cells outside the liver is essential for

the proper functioning of these cells (7). Worldwide, cardiovascular diseases (CVDs) are the leading cause of death. Hypercholesterolemia emerges as a pivotal risk factor in the context of CVDs. Hypercholesterolemia frequently occurs in individuals with diabetes. Atherosclerotic cardiovascular diseases (ASCVDs) are the primary cause of mortality in patients with diabetes. The main role of statins lies in their capacity to impede hepatic cholesterol biosynthesis. Therefore, statin therapy reduces both the incidence and mortality of CVDs by inhibiting cholesterol synthesis. Consequently, this mechanism lowers serum LDL-C levels. (8). Statins exert their effects by reversibly impeding the function of HMG-CoA-R through their interaction with the active site within the mevalonic acid pathway. HMG-CoA-R converts HMG-CoA to mevalonic acid. These agents bear structural resemblance to HMG-CoA and exhibit an augmented propensity to bind to HMG-CoA-R. The obstruction of this pathway impedes cholesterol biosynthesis (9, 10). Only the HMG-CoA-like portion of the statins was similar among them. HMG-CoA-R is a tetramer. It is composed of a pair of dimer units. Each dimer has two active sites. Therefore, this enzyme has four active sites. The enzyme cannot function properly until the dimer forms. Statins interfere with the formation of dimers (11).

Key Differentiating Features of Statins

As explained in the previous section, the inhibition of cholesterol biosynthesis is the primary function of statins. It is worth noting that these statins possess distinct attributes. Statins were divided into two groups: fungal-derived statins and synthetic statins. Fungi-derived statins include lovastatin, pravastatin,

and simvastatin. However, atorvastatin, fluvastatin, pitavastatin, and rosuvastatin are produced via chemical or synthetic methods (12, 13) (**Table 1**). The permeability of membranes varies among different statins. Statins are divided into lipophilic and hydrophilic statins according to their membrane permeability. Lipophilic statins, including atorvastatin, lovastatin, simvastatin, fluvastatin, and pitavastatin, can passively enter both hepatic and nonhepatic cells.

Table 1. Types of statins based on origin and ability to dissolve in water or in lipid-containing media.

Statins	Synthetic	Fungal origin	Lipophilic	Hydrophilic
Atorvastatin	✓		✓	
Fluvastatin	✓		✓	
Lovastatin		✓	✓	
Simvastatin		✓	✓	
Pravastatin		✓		✓
Rosuvastatin	✓			✓
Pitavastatin	✓		✓	

Rosuvastatin and pravastatin exhibit hydrophilic properties with a comparatively abbreviated half-life in contrast to lipophilic statins (**Table 1**). Hydrophilic statins display a selective tendency to permeate hepatocytes and intestinal epithelial cells via active transport facilitated by specialized carriers. So, they exhibit liver- and intestinal epithelial cell-specific affinity. However, these statins are somewhat permeable to other cells. In this regard, organic-anion-transporting polypeptides (OATPs) are

situated within the plasma membrane of hepatocytes and enterocytes. OATPs serve as transporters that facilitate the transfer of hydrophilic statins into liver and intestinal epithelial cells. These transporter proteins possess multifaceted functionality, as they also aid in the transport of organic anions, including bile acids, into hepatic cells in tandem with hydrophilic statins (14). In general, lipophilic statins are more rapidly absorbed, while the kidneys more readily excrete hydrophilic statins. Since most drugs are weak acids or bases, they can exist in two phases in aqueous solution: ionized or polar and unionized or nonpolar. The ionized polar portion is water-soluble, while the unionized portion is lipid-soluble and is the only portion that readily diffuses through cell membranes. Hydrophilic statins can be excreted unchanged. However, the kidney cannot filter lipophilic statins well, and these types of drugs are more likely to be reabsorbed into the tubules. For this reason, most lipophilic statins are metabolized into more polar metabolites that then become water-soluble (15).

In the liver, lipophilic statins exhibit numerous pharmacological interactions with cytochrome P450 (CYP450) isoenzymes and are primarily metabolized by them. Conversely, hydrophilic statins are associated with fewer drug interactions, and the CYP450 system exerts negligible influence on their metabolism (16).

Pitavastatin and pravastatin are less effective than other statins at lowering cholesterol levels (17). Structural differences among statins lead to diverse interactions at the HMG-CoA-R active site, conferring distinct inhibitory properties. So, the

greater effects of rosuvastatin and atorvastatin in lowering cholesterol levels are attributable to their high binding affinity for the HMG-CoA-R enzyme (18). In addition, rosuvastatin has been shown to have greater affinity for HMG-CoA-R than any other statin (4). Even when administered at equivalent doses, rosuvastatin reduces LDL-C levels more than atorvastatin (18). Her et al. showed that rosuvastatin 10 mg/day reduced LDL-C levels in hypercholesterolemic patients more than atorvastatin 20 mg/day (19). In a study conducted by Thongtang et al., rosuvastatin 40 mg/day had a greater effect on lowering LDL-C levels than atorvastatin 80 mg/day in hypercholesterolemic patients (20). Qu and colleagues showed that rosuvastatin (10 mg/day) reduced total cholesterol (TC) and LDL-C more than atorvastatin (10 mg/day) in patients with hypercholesterolemia (21). Furthermore, Yanagi et al. stated that rosuvastatin (2.5 mg/day) lowered LDL-C more than pitavastatin (2 mg/day) in patients with type 2 diabetes mellitus (T2DM) (22). In a study by Soleymani et al., lovastatin 40 mg/day was less effective in reducing LDL-C than atorvastatin 10 mg/day and simvastatin 20 mg/day (23). Also, according to the Adult Treatment Panel III (ATP III), rosuvastatin reduces LDL-C more than other statins (24).

The effects of statins on vascular vasodilation

In addition to cholesterol production, the mevalonate pathway generates isoprenoids, including geranylgeranyl pyrophosphate (GGPP) (25). GPP is a 10-carbon compound that is composed of two isopentenyl pyrophosphate units. Combining two GPP units forms GGPP (26). So, statins hinder the

production of GGPP. Rho family members serve as primary substrates for isoprenylation. GGPP is required for Rho family activation (27). Rho is a member of the Ras GTPase superfamily (28). It participates in vascular complications by initiating downstream effectors, thereby facilitating cellular signal transduction (29). In non-hepatic cells, such as vascular endothelial cells, statins inhibit Rho family GTPases, leading to the accumulation of their inactive forms in the cytoplasm, thereby suppressing vasoconstriction and vascular complications (30, 31).

The role of the Rho family in vasoconstriction

As explained in the previous section, statins block Rho family activity in non-hepatic cells, including vascular endothelial cells, by limiting GGPP production. RhoA is a member of the Rho family more involved in vasoconstriction (32).

RhoA/ROCK pathway and nitric oxide production

The regulation of endothelial nitric oxide synthase (eNOS) in vascular endothelial cells occurs post-translationally (33). In these cells, insulin signaling activates phosphatidylinositol 3-kinase (PI3K). phosphatidylinositol-3, 4, 5-triphosphate (PIP3) triggers PI3K-dependent serine-threonine kinase (PDK1) activation through its role as a second messenger. PDK1 then phosphorylates AKT/PKB. It activates eNOS through phosphorylation at serine (34, 35) (**Figure 1**). Andevvari et al. showed that atorvastatin 20 mg/day elevated serum insulin levels in individuals diagnosed with prediabetes and T2DM. This phenomenon may facilitate the augmentation of eNOS activity (30). Thongtang et al. showed that, in addition to increased insulin concentrations with

atorvastatin 80 mg/day, the maximum dose of rosuvastatin (40 mg/day) also caused significant increases in insulin levels (20).

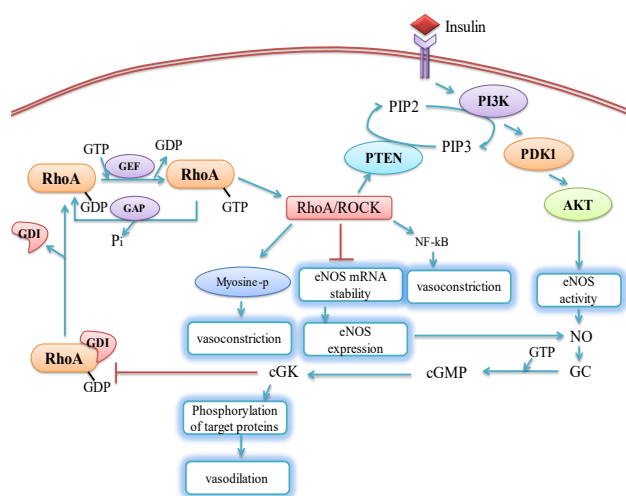


Fig 1. Association between PI3K/AKT/eNOS and RhoA/ROCK with vasoconstriction. Insulin activates eNOS through the PI3K/AKT pathway in endothelial cells. The production of NO ultimately suppresses RhoA/ROCK. RhoA/ROCK destabilizes eNOS, resulting in vasoconstriction and inflammation. **eNOS:** endothelial nitric oxide synthase, **GC:** guanylate cyclase, **cGK:** cGMP-dependent protein kinase, **GDI:** GDP dissociation inhibitor, **GAP:** GTPase-activating protein, **GEF:** guanine-nucleotide exchange factor

Furthermore, Ota et al. declared that statin phosphorylation of Akt at Ser473 increased eNOS expression in human umbilical vein endothelial cells (HUVECs) (36). Jing et al demonstrated that pitavastatin enhanced eNOS generation in HUVECs (37). In a study by Almansob et al., simvastatin 20 mg increased NO production, eNOS expression, and AKT-eNOS activation in patients undergoing noncoronary artery cardiac surgery. Furthermore, this drug reduced p38 signaling pathways in these patients (38). Moreover, Lin et al. declared that atorvastatin 10 mg/day and pitavastatin 2 mg/day enhanced eNOS expression in endothelial progenitor cells (EPCs). But only pitavastatin facilitated eNOS phosphorylation (39). Also, Yemisci and colleagues

stated that pravastatin (40 mg/day) enhanced eNOS activity in human platelets (40) (**Table 2**). Given that statins lower intracellular cholesterol concentrations and that accumulation of cholesterol in lipid rafts on the plasma membrane disrupts insulin signaling (41), statins can thereby improve insulin signaling.

A decline in eNOS synthesis and activity can lead to vascular endothelial dysfunction. RhoA activates RhoA kinase or Rho-dependent kinase (ROCK) (42) (**Figure 1**). ROCK is a kinase belonging to the AGC (PKA/ PKG/PKC) family of serine-threonine-specific protein kinases (43). Phosphatase and tensin homolog (PTEN) is a phosphatase in humans. Mutations in the PTEN gene are a step in the development of many cancers. The RhoA/ROCK pathway suppresses eNOS expression and function through two distinct mechanisms. One of them involves PTEN, which dephosphorylates PI3P. RhoA/ROCK enhances PTEN stability and activates its phosphatase activity via phosphorylation. PTEN negatively regulates AKT activation by dephosphorylating PIP3 to PIP2. Moreover, eNOS mRNA expression can be reduced by ROCK, thereby decreasing eNOS stability and half-life (44). Vascular endothelial cells produce nitric oxide (NO) via eNOS. In vascular smooth muscle cells (VSMCs), NO induces cyclic guanosine monophosphate (cGMP) production by activating guanylate cyclase (GC). Subsequent cGMP-dependent protein kinase (cGK) or protein kinase G (PKG) activation follows. Through phosphorylation of its downstream targets, this kinase reduces intracellular calcium concentration, thereby leading to relaxation of VSM Cs (27, 45).

Table.2. Studies on the effects of statins on vasodilation associated factors

eNOS: endothelial nitric oxide synthase, HUVECs: human umbilical vein endothelial cells, EPCs: endothelial progenitor cells, CAD: coronary artery disease, CHD: congenital heart disease.

Effects on vasodilation associated factors	Model	Doses	Type of statin	Reference
Insulin	in vivo Prediabetes and T2DM patients	20 mg/day	Atorvastatin	(30)
Insulin	in vivo Hyperlipidemic patients	80 mg/day 40 mg/day	Atorvastatin Rosuvastatin	(20)
eNOS expression	in vitro HUVECs	50 and 100 nmol/L	Atorvastatin, pravastatin, and pitavastatin	(36)
eNOS expression	in vitro HUVECs	0.01, 0.1, and 1 μ mol/l	Pitavastatin	(37)
NO production eNOS expression	in vivo Patients undergoing noncoronary artery cardiac surgery	20 mg/day	Simvastatin	(38)
eNOS expression	in vivo EPCs in patients with cardiovascular risk	10 mg/day 2 mg/day	Atorvastatin Pitavastatin	(39)
eNOS activity	in vivo Platelets of patients	40 mg/day	Pravastatin	(40)
NO bioavailability	in vivo Patients with CAD	40 mg/day	Atorvastatin	(49)
eNOS activity	in vitro HUVECs	1 μ mol/l	Fluvastatin	(60)
NO, eNOS	in vivo Patients irresponsive to sildenafil	80 mg/day	Atorvastatin	(61)

NO bioavailability	in vivo Patients with CHD	10 mg/day 20 mg/day	Atorvastatin Simvastatin	(62)
NO bioavailability	in vivo CAD patients	20 mg/day 40 mg/day	Atorvastatin	(63)

The NO/cGMP/cGK pathway exhibits distinct functionality compared with the RhoA/ROCK pathway. As a result, the NO/cGMP/cGK pathway can also impede the RhoA/ROCK signaling pathway. These two pathways can inhibit one another (**Figure 1**). Upon cGK activation, cGK phosphorylates RhoA and binds to a GDP dissociation inhibitor (GDI). Through its interaction with RhoA-bound GDP, GDI impedes the transport of RhoA to the plasma membrane and the binding of guanosine triphosphate (GTP) to RhoA, thereby limiting its activity (27). In the plasma membrane, Rho GTPase activity is regulated by guanine-nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). GEFs are proteins involved in the activation of small GTPases. GEFs facilitate the exchange of GDP for GTP in Rho GTPases, whereas GAPs catalyze the hydrolysis of GTP to GDP. Consequently, GEFs activate Rho GTPases, whereas GAPs deactivate them (46). In addition, ROCK contributes to VSMC contraction by phosphorylating myosin (47). The inhibition of the RhoA/ROCK pathway contributes to the relaxation of VSMCs caused by NO. Statins directly inhibit RhoA and indirectly promote NO production and cGK activation in this pathway (**Figure 1**). Consequently, ROCK is inhibited, and relaxation of VSMCs occurs (48). Antoniades et al. reported that taking atorvastatin in patients with coronary artery disease (CAD) improved vascular NO bioavailability (49). The

RhoA/ROCK pathway also exerts other vasodilation effects in vascular endothelial cells. Notably, ROCK activates the nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B) (48). NF- κ B upregulates endothelin-1 (Et-1) (50). Et-1, upon binding to its receptor in endothelial cells, triggers the proliferation and migration of VSMCs, ultimately leading to vasoconstriction (51). Additionally, this factor may promote atherosclerosis by reactivating NF- κ B (52). Xue et al. showed that atorvastatin attenuated ET-1 levels in patients with leukoaraiosis (53).

Critical Insights into Statin Therapy

Reduced insulin sensitivity, which develops in the presence of inflammation, is a key etiological factor in T2DM (54). Several lines of evidence have suggested that statin therapy may be linked to the onset of T2DM, particularly under specific clinical circumstances (55). Some studies have indicated that statins may exert pro inflammatory effects or be associated with reduced insulin sensitivity and the development of T2DM. According to the Adult Treatment Panel III (ATP III) guidelines, atorvastatin and rosuvastatin are more potent at reducing LDL C levels than other statins (5). Therefore, it is important to consider their potential adverse effects. In a study by Healy et al., peripheral blood monocytes were isolated from patients who were either treated with atorvastatin or not treated. Atorvastatin was shown to upregulate interleukin-1 β (IL 1 β) mRNA and protein levels in macrophages. These results suggest that atorvastatin may promote atherosclerotic plaque calcification through IL 1 β upregulation (56). In a study by Henriksbo et al., atorvastatin treatment of adipose tissue and bone marrow derived

macrophages (BMDMs) from mice inhibited insulin signaling by increasing IL 1 β production and activity (57). Koh and colleagues demonstrated that atorvastatin use in patients with T2DM and metabolic syndrome was significantly associated with decreased insulin sensitivity (58). Consistent with the preceding findings, Moutzouri and colleagues reported that rosuvastatin therapy in hypercholesterolemic patients was associated with a significant increase in insulin resistance (59).

Conclusion

Since lipophilic statins readily enter non-hepatic cells, these statins may improve vasodilation more than hydrophilic statins. The action of statins is due to the inhibition of the production or activity of cholesterol, GGPP, RhoA/ROCK, PTEN, and NF- κ B, and the stimulation of the production or activity of insulin and the PI3K/AKT/eNOS pathway. Considering that rosuvastatin exerts a more potent inhibitory effect on the mevalonate pathway, and given the lipophilic properties of atorvastatin along with its superior inhibition of this pathway relative to other lipophilic statins, these two agents produce a more pronounced vasodilatory effect compared to other statins. Elevating the dose and extending the duration of therapy with these agents may substantially enhance vasodilation. Nevertheless, owing to their potent inhibition of isoprenoid synthesis, the side effects of their use in patients should be considered. Physicians commonly prescribe atorvastatin and rosuvastatin to ameliorate vascular complications. However, these statins are associated with side effects, including inflammation

and decreased insulin sensitivity. Thus, future studies should prioritize additional preclinical and clinical investigations to examine the effects of these agents and compare their effects on vasodilation-related parameters. Such research would help elucidate the precise protective mechanisms of these drugs. Furthermore, for a more detailed exploration of vasodilation-associated mechanisms, studies focusing on endothelial cells and macrophages would be particularly valuable.

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References

1. Endo A. Discovery and Development of Statins. *Natural Product Communications*. 2017;12(8):1934578X1701200801.
2. Alberts AW. Discovery, biochemistry and biology of lovastatin. *The American journal of cardiology*. 1988;62(15):J10-J5.
3. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. *Trials*. 2001;2:1-3.
4. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundamental & clinical pharmacology*. 2005;19(1):117-25.
5. Andevari AN, Qujeq D. Anti-inflammatory Mechanisms Beyond Cholesterol-Lowering Capabilities of Statins: Evidence from in vitro and in vivo Studies. *Advances in Pharmacology and Therapeutics Journal*. 2025.
6. Zerín F, Hasan A, Hasan R. Abstract P002: Mechanism Of Mesenteric Artery Vasodilation And Blood Pressure Regulation By Statins. *Hypertension*. 2022;79(Suppl_1):AP002-AP.
7. Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends in pharmacological sciences*. 1998;19(1):26-37.
8. Brault M, Ray J, Gomez Y-H, Mantzoros CS, Daskalopoulou SS. Statin treatment and new-onset diabetes: a review of proposed mechanisms. *Metabolism*. 2014;63(6):735-45.
9. Andevari AN, Moein S, Qujeq D, Moazezi Z, Tilaki KH. Effects of atorvastatin on concentrations of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase (HMG-CoA-R), proprotein convertase subtilisin/kexin type 9 (PCSK9) and sortilin in patients with type 2 diabetes mellitus and pre-diabetics. *Journal of Nephropathology*. 2020;10(1):e05-e.
10. Andevari AN, Firoozjaee AH, Meftah N, Asciabari HA, Bahri F, Shahandashti NE, et al. The effects of atorvastatin consumption on blood levels of sortilin, glycemic, and lipid indices in type 2 diabetic patients: A randomized clinical trial. *International Journal of Diabetes in Developing Countries*. 2025:1-8.
11. Gesto D, Cerqueira N, Ramos M, Fernandes P. Discovery of new druggable sites in the anti-cholesterol target HMG-CoA reductase by computational alanine scanning mutagenesis. *Journal of molecular modeling*. 2014;20:1-13.
12. Muscogiuri G, Sarno G, Gastaldelli A, Savastano S, Ascione A, Colao A, et al. The good and bad effects of statins on insulin sensitivity and secretion. *Endocrine research*. 2014;39(4):137-43.
13. Sadowska A, Osiński P, Roztocka A, Kaczmarz-Chojnacka K, Zaporá E, Sawicka D, et al. Statins—from fungi to pharmacy. *International Journal of Molecular Sciences*. 2023;25(1):466.
14. Yamazaki M, Suzuki H, Hanano M, Tokui T, Komai T, Sugiyama Y. Na (+)-independent multispecific anion transporter mediates active transport of pravastatin into rat liver. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 1993;264(1):G36-G44.
15. Climent E, Benaiges D, Pedro-Botet J. Hydrophilic or lipophilic statins? *Frontiers in cardiovascular medicine*. 2021;8:687585.
16. Fong CW. Statins in therapy: understanding their hydrophilicity, lipophilicity, binding to 3-hydroxy-3-methylglutaryl-CoA reductase, ability to cross the blood brain barrier and metabolic stability based on electrostatic molecular orbital studies. *European journal of medicinal chemistry*. 2014;85:661-74.

17. Agouridis AP, Kostapanos MS, Elisaf MS. Statins and their increased risk of inducing diabetes. *Expert Opinion on Drug Safety*. 2015;14(12):1835-44.
18. White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *The Journal of Clinical Pharmacology*. 2002;42(9):963-70.
19. Her A-Y, Kim J-Y, Kang S-M, Choi D, Jang Y, Chung N, et al. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. *Journal of Cardiovascular Pharmacology and Therapeutics*. 2010;15(2):167-74.
20. Thongtang N, Ai M, Otokozawa S, Himbergen TV, Asztalos BF, Nakajima K, et al. Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation. *The American journal of cardiology*. 2011;107(3):387-92.
21. Qu H-y, Xiao Y-w, Jiang G-h, Wang Z-y, Zhang Y, Zhang M. Effect of atorvastatin versus rosuvastatin on levels of serum lipids, inflammatory markers and adiponectin in patients with hypercholesterolemia. *Pharmaceutical research*. 2009;26:958-64.
22. Yanagi K, Monden T, Ikeda S, Matsumura M, Kasai K. A crossover study of rosuvastatin and pitavastatin in patients with type 2 diabetes. *Advances in therapy*. 2011;28:160-71.
23. SOLEYMANI A, NIKOUEINEZHAD H, TABATABAEIZADE M, Mianehsaz E, TAMADON M. Effect of hydroxymethylglutaryl-CoA reductase inhibitors on low-density lipoprotein cholesterol, interleukin-6, and high-sensitivity C-reactive protein in end-stage renal disease. 2011.
24. Ohsfeldt RL, Gandhi SK, Fox KM, Stacy TA, McKenney JM. Effectiveness and cost-effectiveness of rosuvastatin, atorvastatin, and simvastatin among high-risk patients in usual clinical practice. *Am J Manag Care*. 2006;12(15 Suppl):S412-23.
25. Conart C, Bomzan DP, Huang X-Q, Bassard J-E, Paramita SN, Saint-Marcoux D, et al. A cytosolic bifunctional geranyl/farnesyl diphosphate synthase provides MVA-derived GPP for geraniol biosynthesis in rose flowers. *Proceedings of the National Academy of Sciences*. 2023;120(19):e2221440120.
26. Chang HY, Cheng TH, Wang AHJ. Structure, catalysis, and inhibition mechanism of prenyltransferase. *IUBMB life*. 2021;73(1):40-63.
27. Sawada N, Liao JK. Rho/Rho-associated coiled-coil forming kinase pathway as therapeutic targets for statins in atherosclerosis. *Antioxidants & redox signaling*. 2014;20(8):1251-67.
28. Mosaddeghzadeh N, Ahmadian MR. The RHO family GTPases: mechanisms of regulation and signaling. *Cells*. 2021;10(7):1831.
29. Nunes KP, Webb RC. New insights into RhoA/Rho-kinase signaling: a key regulator of vascular contraction. *Small GTPases*. 2021;12(5-6):458-69.
30. Nosrati Andevari A, Qujeq D, Hajian-Tilaki K. The Effects of Atorvastatin Consumption on Biochemical Variables in Patients with Type 2 Diabetes Mellitus and Pre-diabetes. *International Journal of Medical Laboratory*. 2022;9(3):198-208.
31. Andevari AN, Moein S, Qujeq D, Moazezi Z, Tilaki KH. The effect of atorvastatin on the concentrations of methylglyoxal, glyoxalase 1, and aldo-keto reductase family 1 member B10 in patients with type 2 diabetes mellitus and prediabetes. *International Journal of Diabetes in Developing Countries*. 2023;1-9.
32. Zhang D, Chang S, Jing B, Li X, Shi H, Zheng Y, et al. Reactive oxygen species are essential for vasoconstriction upon cold exposure. *Oxidative Medicine and Cellular Longevity*. 2021;2021(1):8578452.
33. Guerby P, Tasta O, Swiader A, Pont F, Bujold E, Parant O, et al. Role of oxidative stress in the dysfunction of the placental endothelial nitric oxide synthase in preeclampsia. *Redox biology*. 2021;40:101861.
34. Tan J, Li X, Dou N. Insulin resistance triggers atherosclerosis: caveolin 1 cooperates with PKC ζ to block insulin signaling in vascular endothelial cells. *Cardiovascular Drugs and Therapy*. 2024;38(5):885-93.
35. Schwartz KS, Hernandez PV, Maurer GS, Wetzel EM, Sun M, Jalal DI, et al. Impaired microvascular insulin-dependent dilation in women with a history of gestational diabetes. *American Journal of Physiology-Heart and Circulatory Physiology*. 2024;327(4):H793-H803.
36. Ota H, Eto M, Kano MR, Kahyo T, Setou M, Ogawa S, et al. Induction of endothelial nitric oxide synthase, SIRT1, and catalase by statins inhibits endothelial senescence through the Akt pathway. *Arteriosclerosis, thrombosis, and vascular biology*. 2010;30(11):2205-11.
37. Jing C, Guo M, Bao X, Li T, Lin J, Lu X, et al. Pitavastatin up-regulates eNOS production by suppressing miR-155 expression in lipopolysaccharide-stimulated human umbilical vein endothelial cells. *Cardiovascular Therapeutics*. 2017;35(5):e12282.
38. Almansob MAS, Xu B, Zhou L, Hu X-X, Chen W, Chang F-J, et al. Simvastatin reduces myocardial injury undergoing noncoronary artery cardiac surgery: a randomized controlled trial. *Arteriosclerosis, thrombosis, and vascular biology*. 2012;32(9):2304-13.
39. Lin L-Y, Huang C-C, Chen J-S, Wu T-C, Leu H-B, Huang P-H, et al. Effects of pitavastatin versus atorvastatin on the peripheral endothelial progenitor cells and vascular endothelial growth factor in high-risk patients: a pilot prospective, double-blind, randomized study. *Cardiovascular diabetology*. 2014;13:1-11.
40. Yemisci M, Ay H, Kocaefe Ç, Qui J, Topalkara K, Özgüç M, et al. Statin potentiates human platelet eNOS activity without enhancing eNOS mRNA and protein levels. *Cerebrovascular diseases*. 2008;26(2):190-8.
41. Taghibiglou C, Bradley CA, Gaertner T, Li Y, Wang Y, Wang YT. Mechanisms involved in cholesterol-induced neuronal insulin resistance. *Neuropharmacology*. 2009;57(3):268-76.

42. Iyer M, Subramaniam MD, Mankatesan D, Cho S-G, Ryding M, Meyer M, et al. Role of RhoA-ROCK signaling in Parkinson's disease. *European journal of pharmacology*. 2021;894:173815.
43. Liu J, Wada Y, Katsura M, Tozawa H, Erwin N, Kapron CM, et al. Rho-associated coiled-coil kinase (ROCK) in molecular regulation of angiogenesis. *Theranostics*. 2018;8(21):6053.
44. Rikitake Y, Liao JK. Rho GTPases, statins, and nitric oxide. *Circulation research*. 2005;97(12):1232-5.
45. Zhao Y, Vanhoutte PM, Leung SW. Vascular nitric oxide: Beyond eNOS. *Journal of pharmacological sciences*. 2015;129(2):83-94.
46. Van Aelst L, D'Souza-Schorey C. Rho GTPases and signaling networks. *Genes & development*. 1997;11(18):2295-322.
47. Brown JH, Del Re DP, Sussman MA. The Rac and Rho hall of fame: a decade of hypertrophic signaling hits. *Circulation research*. 2006;98(6):730-42.
48. Jeong K, Park S, Cho K, Sohn J, Lee J, Kim Y, et al. The Rho/ROCK pathway for lysophosphatidic acid-induced proteolytic enzyme expression and ovarian cancer cell invasion. *Oncogene*. 2012;31(39):4279-89.
49. Antoniadou C, Bakogiannis C, Leeson P, Guzik TJ, Zhang M-H, Tousoulis D, et al. Rapid, direct effects of statin treatment on arterial redox state and nitric oxide bioavailability in human atherosclerosis via tetrahydrobiopterin-mediated endothelial nitric oxide synthase coupling. *Circulation*. 2011;124(3):335-45.
50. Wang X-H, Ao Q-G, Cheng Q-L. Caloric restriction inhibits renal artery ageing by reducing endothelin-1 expression. *Annals of Translational Medicine*. 2021;9(12).
51. Carreño JE, Apablaza F, Ocaranza MP, Jalil JE. Cardiac hypertrophy: molecular and cellular events. *Revista Española de Cardiología (English Edition)*. 2006;59(5):473-86.
52. Sobrano Fais R, Menezes da Costa R, Carvalho Mendes A, Mestriner F, Comerma-Steffensen SG, Tostes RC, et al. NLRP3 activation contributes to endothelin-1-induced erectile dysfunction. *Journal of Cellular and Molecular Medicine*. 2023;27(1):1-14.
53. Xue J, Wu Z, Gong S, Qin S, Gu A. High-dose atorvastatin improves vascular endothelial function in patients with leukoaraiosis. *Journal of Clinical Laboratory Analysis*. 2020;34(3):e23081.
54. Andevare AN, Shahandashti NE, Koolivand M, Bahri F, Douseh R, Qujeq D. Biochemical and Biological Properties of Curcumin and its Association with Carbohydrate Metabolism: A Review Article. *Journal of Basic Research in Medical Sciences*. 2026;13(3):61.
55. Laakso M, Fernandes Silva L. Statins and risk of type 2 diabetes: mechanism and clinical implications. *Frontiers in endocrinology*. 2023;14:1239335.
56. Healy A, Berus JM, Christensen JL, Lee C, Mantsounga C, Dong W, et al. Statins disrupt macrophage Rac1 regulation leading to increased atherosclerotic plaque calcification. *Arteriosclerosis, thrombosis, and vascular biology*. 2020;40(3):714-32.
57. Henriksbo BD, Tamrakar AK, Phulka JS, Barra NG, Schertzer JD. Statins activate the NLRP3 inflammasome and impair insulin signaling via p38 and mTOR. *American Journal of Physiology-Endocrinology and Metabolism*. 2020;319(1):E110-E6.
58. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *Journal of the American College of Cardiology*. 2010;55(12):1209-16.
59. Moutzouri E, Liberopoulos E, Mikhailidis D, Kostapanos M, Kei A, Milionis H, et al. Comparison of the effects of simvastatin vs. rosuvastatin vs. simvastatin/ezetimibe on parameters of insulin resistance. *International journal of clinical practice*. 2011;65(11):1141-8.
60. Aoki C, Nakano A, Tanaka S, Yanagi K, Ohta S, Jojima T, et al. Fluvastatin upregulates endothelial nitric oxide synthase activity via enhancement of its phosphorylation and expression and via an increase in tetrahydrobiopterin in vascular endothelial cells. *International journal of cardiology*. 2012;156(1):55-61.
61. El-Sisi A, Hegazy S, Salem K, AbdElkawy K. Atorvastatin improves erectile dysfunction in patients initially irresponsive to Sildenafil by the activation of endothelial nitric oxide synthase. *International journal of impotence research*. 2013;25(4):143-8.
62. Li J, Sun YM, Wang LF, Li ZQ, Pan W, Cao HY. Comparison of effects of simvastatin versus atorvastatin on oxidative stress in patients with coronary heart disease. *Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease*. 2010;33(4):222-7.
63. Liu L, Gao L, Tan H, Qi Y, Cui D, Wang Z, et al. Effect of different doses of atorvastatin on collateral formation in coronary artery disease patients with coronary atherosclerosis. *Coronary Artery Disease*. 2022;33(6):473-8.