Journal of Research in Clinical Medicine

J Res Clin Med, 2023, 11: 3
doi: 10.34172/jrcm.2023.32150
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Reviews

A review on statins with a focus on type 2 diabetes

Vahideh Sadra[1#], Mitar Niafar[1#], Vahid Hosseini[2], Amir Mehdizadeh[3*]

[1]Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Biochemistry and Clinical Laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[#]Both authors contributed equally to this work

Article info

Article History:
Received: September 11, 2021
Accepted: January 26, 2022
e-Published: February 26, 2023

Keywords:
Diabetes mellitus, Statins, Hypercholesterolemia, Cardiovascular diseases, Inflammation, Coagulation factors

Abstract

Statins are the most important lipid lowering drugs and their protective effects in primary or secondary cardiovascular diseases (CVDs) have been well documented. However, various number of evidences have revealed that the beneficial effects of statins regarding the CVDs are not only due to their blood cholesterol lowering properties but also because of their pleiotropic effects such as inhibition of isoprenoids synthesis, immunomodulation and neuroprotection. Type 2 diabetes mellitus (T2DM) is a systemic disease with inflammatory properties and micro/macro-vascular complications. Despite the beneficial effects of statins to lower blood cholesterol level, mortality decrease due to CVD and stroke, dyslipidemia improvement, and their anti-inflammatory and anti-coagulatory properties have not well been studied, especially in T2DM. In this review, we discuss the pharmacology, pleiotropic effects, dose prescribing and side effects of statins with a focus on type 2 diabetes.

Introduction

Dyslipidemia is an important clinical complication in patients with diabetes mellitus. Clinical manifestations of diabetic dyslipidemia are high triglyceride (TG) level, low concentration of high density lipoprotein-cholesterol (HDL-C) and increased small dense low-density lipoprotein (sdLDL-C). In this regard, insulin resistance causes free fatty acids (FFAs) mobilization from adipose tissue into liver, leading to increased TG production and consequently accumulation of large TG-rich very low-density lipoprotein (VLDL) and sdLDL particles production, as well.[1] Hence, even when LDL-C levels is not increased in type 2 diabetic patients, increased atherogenic sdLDL is usually observed.[1] Cholesterol is an essential component of cell membranes and a precursor for bile salts and steroid hormones synthesis. Both endogenous and exogenous cholesterols are transported to peripheral tissues by apoB-containing plasma lipoproteins including HDL-C and LDL-C.[2] However, circulating LDL-C cannot be directly contributed in diabetes-related atherosclerosis process and apoB action as a ligand for atrial wall monocyte-macrophage scavenger receptors initiate foam cells formation [3]. In this regard, statins discovery, as lipid-lowering drugs, has led to remarkable advances in the cardiovascular medicine. Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, as the rate-limiting enzyme in cholesterol biosynthesis.[3] Obtained evidences from clinical trials show that cholesterol lowering by statins have resulted in the decreased coronary heart disease (CHD) and stroke in people with or without pre-existing cardiovascular diseases (CVDs).[4-6]

In addition to lipid lowering properties, statins exert anti-inflammatory activities via C-reactive protein, chemokines, cytokines, and adhesion molecules reduction, as well as T-cell activity modulation.[7] Moreover, statins also inhibit leukocytes transendothelial migration through decreased expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1, lymphocyte function-associated antigen-1, and monocyte chemotactic protein-1. On the other hand, statins suppress inflammatory responses by inhibition of chemokine release and Th1-type chemokine receptors on T cells.[8,9]

Treatment of patients with statins can also significantly downregulate the blood coagulation cascade, which is most probably due to the decreased tissue factor expression, leading to reduced thrombin production. Additionally, statins use has been associated with the impaired several coagulation reactions catalyzed by HMG-CoA reductase enzyme. Moreover, statins may enhance the protein C anticoagulant pathway activity via the increased expression of thrombomodulin on the

***Corresponding Author:** Amir Mehdizadeh, Email: mehdizadeha@tbzmed.ac.ir

endothelial cells. Most of the antithrombotic effects of statins are also implicated in inhibition of isoprenylation of signaling proteins. These novel properties of statins suggest that these agents may potentially act as mild anticoagulants, which is observed in a wide spectrum of patients with varying cholesterol levels, including diabetic patients.[10]

Regarding the pleiotropic effects of statins, this article aimed to review the mechanism of action, beneficial and side effects of statins with a focus on type 2 diabetes mellitus (T2DM).

Methods

The inclusion criteria were as follows: (1) Original, narrative and systematic reviews and meta-analysis, and retrospective and prospective cohort studies, (2) studies using different types and doses of statins, (3) studies with different age and sex groups, and (4) studies published in English language.

The exclusion criteria were as follows: (1) Lack of access to full text of the article, (2) Case report studies, (3) Animal studies, and (4) history of malignancy and inflammatory diseases.

In order to achieve desired studies, electronic databases including PubMed, Embase, Scopus, Web of Science, and ProQuest were searched. Article searches were performed using systematic search with MeSH keywords and in combination with OR and AND operators. The keywords "diabetes mellitus", "statins", "hypercholesterolemia", "cardiovascular diseases", "inflammation", and "coagulation factors" were used to search the literature. The Google Scholar search engine and the list of references of review articles were then reviewed to identify more articles. Published studies from 1 Jan 2000 to 1 Jan 2021 were included. To select articles, titles and abstracts of articles were independently reviewed by three researchers. The full text of eligible articles was retrieved and screened by the mentioned researchers using inclusion and exclusion criteria. The articles which did not meet the inclusion criteria were excluded. At all stages of the articles selection, in case of any disagreement, an agreement was reached with the discussion and participation of the fourth researcher.

Statins category and mechanisms of action

HMGCoA reductase inhibition

Liver is one of the target organs in which HMGCoA reductase, the enzyme catalyzing the conversion of HMGCoA to mevalonic acid as a cholesterol precursor, is inhibited by statins. Statins compete with the normal HMGCoA reductase substrate on enzyme active site and prevent the enzyme from adopting induced functional conformation. This property makes statins an effective and specific drug for controlling the cholesterol synthesis. Moreover, statins reversibly bind to the active site with the affinity in the nanomolar range (the normal substrate has the micromolar affinity).[11] HMGCoA reductase inhibition promotes the translocation of sterol regulatory element binding proteins (SREBPs)-slicing protease from endoplasmic reticulum into the nucleus leading to the increased LDL-receptor expression. On the other side, the decreased cholesterol synthesis in hepatocytes following statins' administration, further increases the LDL-receptor expression, leading to the lowered circulating LDL-C and its precursors including intermediate density lipoprotein (IDL) and VLDL.[12] Moreover, statins inhibit the hepatic synthesis of apolipoprotein B_{100}, resulting in TG containing lipoproteins decrease and Apo B/E receptors production increase.[13,14] Statins also slightly increase the HDL-C level and have no effect on lipoprotein (a) concentration.[15] Table 1 represents the general characteristics and bioavailability of statins in human body. Figure 1 also illustrates the proposed mechanisms for statins anti-oxidative properties.

Mechanisms affecting intracellular pathways by isoprenoids synthesis inhibition

statins administration arrests the synthesis of some isoprenoids such as isopentenyl adenosine (present in a group of tRNAs), dolicholes (required for glycoproteins synthesis) and poly-isoprenoid side-chains of ubiquinone and heme A (involved in electron transfer chain) and affects the related cellular signaling pathways during mevalonate synthesis.[21]

A variety of proteins possess a group of isoprenoid residues mainly in the form of C15 farnesyl and C20 geranylgeranyl. The most common isoprenylation site in these proteins is the C-terminal region as "CaaX", in which "C" represents for cysteine, "a" is often an aliphatic amino acid and "X" can be any amino acid.[19] Proteins are farnesylated when "X" is one of the alanine, methionine or serine amino acids and geranylgeranylated when "X" is leucine.[19]

Many of prenylated proteins are in interaction with intracellular membranes and any mutation in cysteine causes blocking the membrane localization of these proteins. The hydrophobic prenylated group can anchor carrying protein to the membrane leading to the establishment of protein-protein interactions required for complex intracellular signaling pathways and communications.[19] In this regard, the extracellular water-soluble signaling molecules are bonded to the specific receptors of cell and corporate the extracellular signals with intracellular signaling pathways. Interestingly, many of these signaling proteins act in prenylated form. The specific receptors of cell surface membranes are usually associated with trimeric G protein or exhibit Ser/Thr/Tyr kinase activity. This trimeric G protein contains a geranylgeranylated (gamma) subunit, allowing this protein to enter into cell membrane near the specific receptors. Then, these extracellular signals are transduced to the intracellular secondary signaling molecules.[21] Ras family components are another crucial category

Table 1. General metabolic characteristics and bioavailability of statins in human body

Metabolic characteristics		Reference
Retained dose by liver (%)		
Fluvastatin and lovastatin	70	
Simvastatin	80	16
Pravastatin	46	
Atorvastatin and cerivastatin	NA	
Half life (h)		
Pitavastatin	12	
Atorvastatin	15-30	
Rosuvastatin	19	17
Simvastatin	2-3	
Pravastatin	1.3-2.8	
Fluvastatin	0.5-2.3	
Metabolization pathways		
Lovastatin/Cerivastatin	Cyt P450	
Simvastatin	CYP3A4, 3A5	
Atorvastatin	CYP3A4	17,18
Fluvastatin/pitavastatin/rosuvastatin	CYP 2C9	
Pravastatin	-	
Bioavailibility (%)		
Atorvastatin	12	
Pravastatin	18	
Rosuvastatin	20	17,19
Fluvastatin	19-29	
Simvastatin and lovastatin	5	
Cerivastatin/pitavastatin	60	
Physio-chemical properties		
Pravastatin/rosuvastatin	Hydrophilic	
Fluvastatin/simvastatin/atorvastatin/ pitavastatin/ lovastatin/cerivastatin	Lipophilic	17
Binding to proteins (%)		
Pitavastatin/fluvastatin	>99	
Atorvastatin	80-90	
Rosuvastatin	88	17
Simvastatin	94-98	
Pravastatin	43-55	
Urinary excretion (%)		
Pitavastatin	<2	
Atorvastatin	2	
Rosuvastatin	10	17
Simvastatin	13	
Pravastatin	20	
Fluvastatin	6	
Fecal excretion (%)		
Pitavastatin	80	
Atorvastatin	70	
Rosuvastatin	90	17
Simvastatin	58	
Pravastatin	71	
Fluvastatin	90	
Specific activity		
Atorvastatin	Active compounds (Acidic)	
cerivastatin	Active compounds (Acidic)	
fluvastatin	Active compounds (Acidic)	20
pravastatin	Active compounds (Acidic)	
Lovastatin	Inactive forms (lactone)	
simvastatin	Inactive forms (lactone)	
Interactions with drugs leading to increased risk of toxicity		
Pitavastatin	Diclofenac, amiodarone, azole antifungals, protease inhibitors, metronidazole, gemfibrozil	
Atorvastatin	Amiodarone, grapefruit juice, protease inhibitors, azole antifungals, macrolide antibiotics, verapamil, cyclosporin, sildenafil, tacrolimus, colchicine	
Rosuvastatin	Diclofenac, amiodarone, azole antifungals, protease inhibitors, metronidazole, gemfibrozil	17
Simvastatin	Amiodarone, Grapefruit juice, protease inhibitors, azole antifungals, macrolide antibiotics, verapamil, cyclosporin, sildenafil, tacrolimus, colchicine	
Pravastatin	Colchicine, gemfibrozil	
Fluvastatin	Diclofenac, amiodarone, azole antifungals, protease inhibitors, metronidazole, gemfibrozil	

NA, not available.

of prenylated signaling proteins and mediate the Ser/Thr/Tyr kinase activity of the cell membrane surface receptors[21] (Figure 2).

Statins and diabetes

Effect on lipid profile

Dyslipidemia is an important biochemical disorder in T2DM patients, which is independently associated with increased morbidity and mortality due to CVDs.[22] These lipid abnormalities include the elevated blood TG levels in fasting and postprandial states, the decreased HDL-C level, the normal or slightly elevated LDL-C concentration, and the increased number of sdLDL particles. Moreover, Apo B level, as a carrier protein in LDL-C and VLDL, is also increased. FFAs mobilization from adipose tissue, as well as impaired insulin-mediated skeletal muscle uptake of FFAs lead to the increased circulating FFAs and hepatic fatty acids influx and consequently TG formation.[22]

In 2005, Cholesterol Treatment Trialists' (CTT) Collaboration performed a prospective meta-analysis study on obtained data from 14 randomized clinical trial studies including 90056 individuals.[23] This study reported a significant reduction in LDL-C level (0.8 mmol/L) and

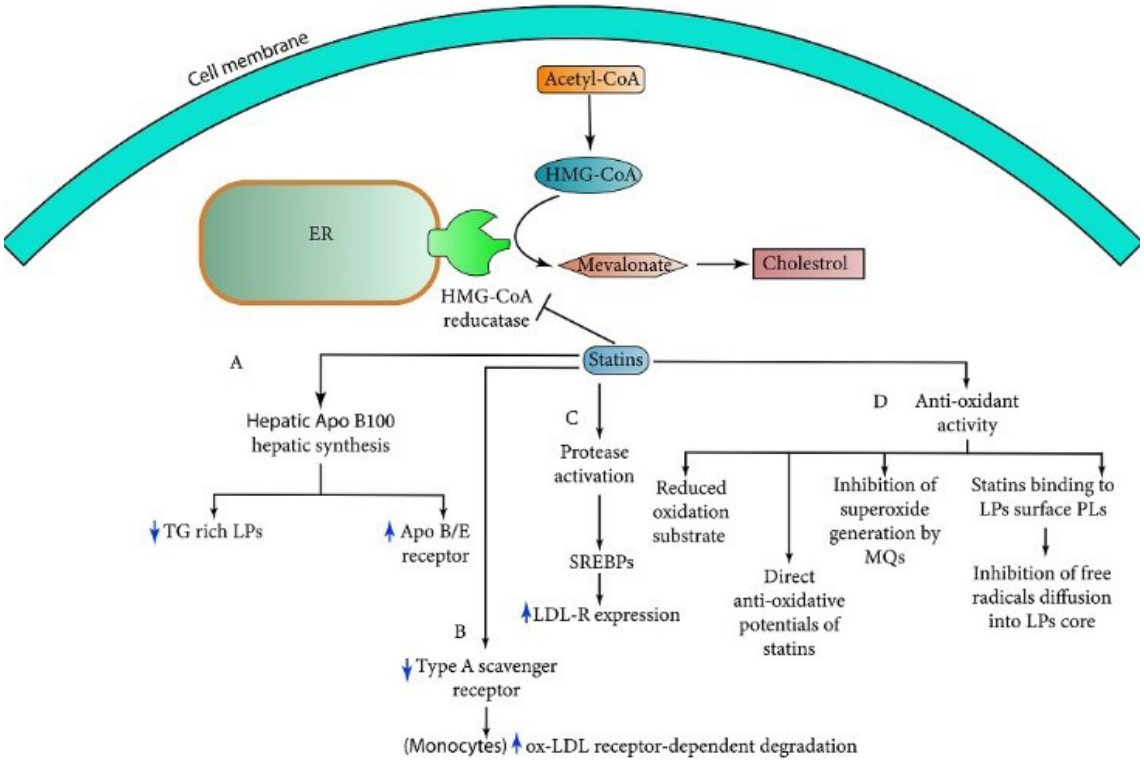

Figure 1. Statins biological effects following HMGCoA reductase inhibition. **(A)** Inhibitory effect on hepatic Apo B100 synthesis causes decreased production of TG-rich LPs and increased production of ApoB/E, (**B)** Decreased expression of Type A scavenger receptor following statin therapy leads to increased ox-LDL receptor-dependent degradation, (**C)** Statins can upregulate LDL receptor through SREBPs and (**D)** anti-oxidant activities of statins are mediated by reduced oxidation substrate, direct anti-oxidative properties, MQs-dependent inhibition of superoxide generation and inhibition of free radicals diffusion into LPs core. HMGCoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; ER: endoplasmic reticulum; TG: triglyceride; PLs: phospholipids; LPs: lipoproteins; LDL-R: low density lipoprotein receptor; ox-LDL: oxidized LDL; SREBPs: sterol regulatory element-binding proteins; MQs: macrophages

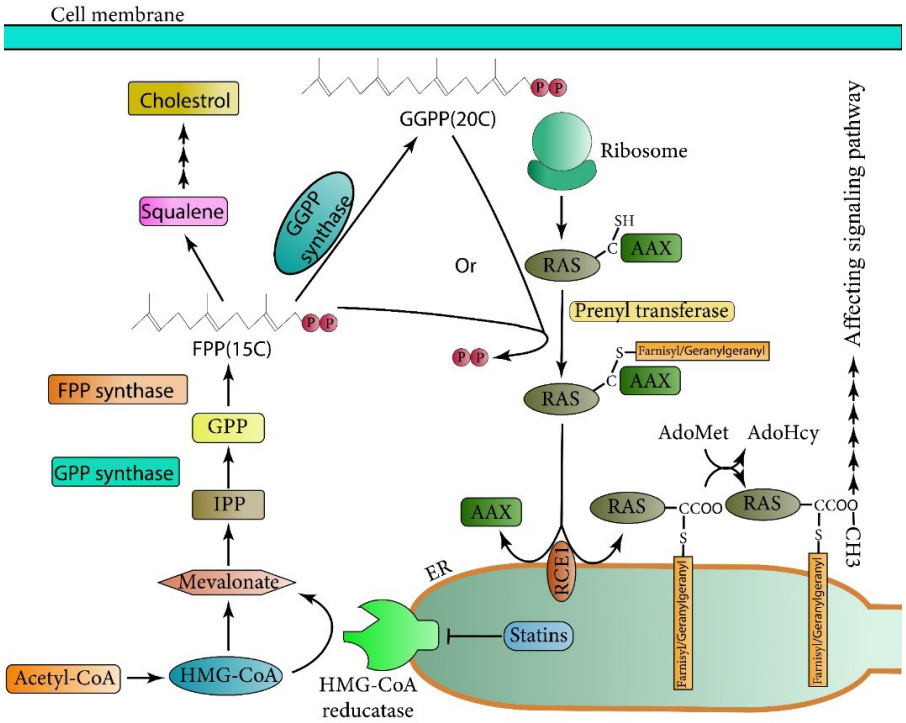

Figure 2. Statins can affect cellular signaling pathways by HMGCoA reductase. FPP production is the initial step of cholesterol synthesis by the intermediary effect of squalene synthase. However, this component can eventually be converted to GGPP by GGPP synthase. Alternatively, FPP and GGPP by the activity of prenyl transferase bind to the CAAX motif of targeted proteins (such as RAS) to complete the protein prenylation process. Then, protein prenylation is occurred in the cytoplasmic side of the ER, which can affect the cellular signaling pathways. HMGCoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; IPP: isopentyl diphosphate; GPP: geranyl pyrophosphate; FPP: farnesyl pyrophosphate; GGPP: geranylgeranyl pyrophosphate; RCE1: RAS-converting CAAX endopeptidase 1; ICMT: isoprenyl-cysteine carboxyl methyltransferase; AdoMet: S-adenosyl methionine

CVD risk during 5 years. Moreover, CTT collaboration also showed that 1 mmol/L reduction in LDL-C causes 23% reduction in CV events. Therefore, patients with T2DM further benefit from statin therapy compared to non-diabetic counterparts.

In 2010, CTT collaboration conducted additional studies on intensive cholesterol lowering by statin therapy. Data revealed a 15% reduction in major vascular events compared to statin standard regimens, so that the mean LDL-C reduction was 0.5 mmol/L after 1 year of administration.[24] However, these findings were also associated with the increased statins side effects which encouraged CTT collaboration to publish a report on statins safety and tolerability.[25]

Regarding the other serum lipid components, Branchi et al[26] in a study reported similar effects of atorvastatin (10 mg) and simvastatin (20 mg) on serum TG, total cholesterol (TC), and LDL-C reduction and HDL-C increase in patients with hypercholesterolemia. In this report, simvastatin exhibited greater effects than that of atorvastatin. Due to these reasons, statins are considered as the first-line drugs in the treatment of T2DM.

Effects on the inflammatory factors

Observational researches reported the first evidence regarding the probable relationship between inflammation and diabetes.[27] About a century ago, high dose administration of sodium salicylate in diabetes suspected individuals led to the decreased glycosuria.[28,29] Later, further studies revealed that this hypoglycemic property was due to the serine kinase IkappaB kinase beta inhibition, which is in relation with insulin post-receptor action.[30] In 1993, Hotamisligil et al[31] in a study on inflammation and diabetes reported the role of tumor necrosis factor (TNF)-α in obesity and insulin resistance. Other epidemiological investigations further indicated the elevated level of inflammatory markers and acute-phase proteins including fibrinogen, C-reactive protein (CRP), interleukin (IL)-6, plasminogen activator inhibitor 1, acid sialic, and white blood cells. [32-34]

Muhlestein et al[35] in a study on 300 T2DM patients receiving simvastatin (20 mg) or fenofibrate (160 mg) or both reported a significant reduction in hs-CRP and lipoprotein associated-phospholipase A2 level after 12 weeks of simvastatin administration. Similar effects were also observed regarding the fenofibrate. However, no significant difference was observed between two groups.

Similarly, Niafar et al[36] in a recent study on 150 T2DM patients receiving 10 mg (n = 74) or 40 mg (n = 76) atorvastatin also observed a significant reduction in the inflammatory markers including hs-CRP, IL-1 and IL-6 after 12 weeks of treatment compared to the baseline level. However, greater effects were observed following 40 mg atorvastatin prescribing.

Tan et al[37] showed that atorvastatin (10 mg/d) use for 12 weeks did not significantly lower CRP levels in T2DM patients. However, 20 mg/d administration for an additional three months led to the significant reduction in the CRP levels compared to the placebo group. Additionally, an improvement in endothelial-dependent vasodilatation was also observed in the mentioned patients.

Diabetes Atorvastatin Lipid Intervention (DALI) study[38] also showed that 80 mg/d of atorvastatin causes a significant reduction (-47%) in CRP level; however, 10 mg/d of atorvastatin only had significant effects in patients with baseline CRP levels > 3 mg/L. Moreover, 80 mg/d of atorvastatin had a more potent effect on CRP levels compared to 10 mg/d of atorvastatin or placebo.

Effect on coagulation

T2DM is usually associated with blood coagulation alteration such as clot structure, clot formation kinetics and its lysis.[39] Several factors such as concentration and activity changes of coagulation proteins are responsible for this process, which cause the defective thrombin production and fibrin clot molecular structure changes.[39] Table 2 summarizes the altered coagulation proteins concentration in T2DM.

Different studies have also reported the probable anti-thrombogenesis effect of statins in patients with T2DM.[55,56] Ferroni et al[57] in a study on 198 patients with chronic T2DM under statin therapy (40 mg/d atorvastatin, n = 57; 40 mg/d simvastatin, n = 22 and 10 mg/d rosuvastatin, n = 14) or not (n = 105), reported a condition of hypercoagulability in T2DM patients not treated with oral statins compared to statin-treated counterparts. Park et al[58] in a moderate statin-therapy program on 25 T2DM patients (simvastatin 20 mg/d, atorvastatin 10-20 mg/d, rosuvastatin 5-10 mg/d, pitavastatin 2 mg/d, or pravastatin 40 mg/d) for 3 months observed a significantly reduced endogenous thrombin potential (ETP) compared to the pre-treatment level; however, prothrombin time (PT), activated partial thromboplastin time (aPTT) and neutrophil extracellular traps (NET) did not show any significant changes. Furthermore, statin therapy not only reduced the coagulation factors including factor II, V, VIII, IX and X, but also it reduces the anti-thrombin as an anticoagulation factor. Reduction of factor V and X following statin-therapy also significantly contributed to the ETP value reduction.

Sommeijer et al[59] also reported a significant reduction in F1.2, von Willebrand factor (vWF), and soluble tissue factor in T2DM patients treated with 40 mg/d pravastatin for 8 weeks compared to pretreatment status. However, Fibrinogen and D-dimer levels showed no significant changes.

Fattah et al[60] in a study on 30 patients with T2DM randomly allocated for treatment with aspirin (100 mg/d, n = 7), atorvastatin (40 mg/d, n = 8), both (n = 7) or not

(n = 8), observed a reduced thrombotic risk assessed by TG after atorvastatin (but not aspirin) therapy.

In a recent study conducted by Niafar et al[36] 10 mg/d versus 40 mg/d doses of atorvastatin were compared in T2DM patients. Data showed a significant reduction in fibrinogen level after 12 weeks of statin therapy, so that 40 mg/d had a greater reducing effect. However, no significant difference was observed regarding the homocysteine before and after statin therapy in the mentioned groups.

Table 2. Alteration pattern of coagulatory proteins in type 2 diabetes

Proteins	Factors	Reference
Pro-coagulant proteins	↑ vWF	40
	↑ kininogen	41
	↑ kallikrein	39
	↑ soluble tissue factor	42
	↑ factor V	43
	↑ (activated) factor VII	42
	↑ factor VIII	44
	↑ factor IX	44
	↑ factor X	43
	↑ factor XI	39
	↑ (activated) factor XII	45
	↑ factor XIII	46
	↑ prothrombin	43
	↑ fibrinogen	47
Anticoagulant proteins	↑ antithrombin,	44
	↓ antithrombin	39
	↓ antithrombin activity with bad glycaemic control	48
	↓ protein C	49
	↓ protein C activity with bad glycaemic control	48
	↓ protein S	50
	↓ protein S activity with bad glycaemic control	48
	↑ tissue factor pathway inhibitor	42
	↑ thrombomodulin	49
Pro-fibrinolytic proteins	↑ tissue plasminogen activator	51
Anti-fibrinolytic proteins	↑ PAI-1	40, 47, 52
	↑ α2-antiplasmin	52
	↑ thrombin-activatable fibrinolysis inhibitor	53
	↑ α2-maroglobulin	54

vWF, von Willebrand factor; PAI-1, Plasminogen activator inhibitor-1.

Statins dose administration

Life-style changes including weight loss, increased physical activity, and nutrition therapy should be considered as the first decision for lowering the risk of atherosclerotic cardiovascular disease (ASCVD) in T2DM.[61] In addition to life-style changes, statin therapy is a critical strategy to control the ASCVD risk in diabetic patients; however, recent American College of Cardiology (ACC), American Heart Association (AHA) and American Diabetic Association (ADA) guidelines have proposed that not all diabetic patients need statin therapy regarding the serum cholesterol level. Based on these recommendations, diabetic patients aged 40 to 75 with LDL-C > 70 mg/dL, should start the statin therapy. Additionally, in patients with LDL-C < 70 mg/dL if the 10-year risk of ASCVD score was more than 7.5%, the statin therapy may be beneficial.[62] Similarly, patients aged 40 to 75 with ASCVD risk > 7.5% should also be considered for high dose statin therapy for the secondary prevention according to Cholesterol Treatment Trialists' Collaboration.[63] Patients aged < 40 or > 75 years should be analyzed for the risks and benefits of statin-based therapy[63] (Table 3).

On the other side, American Association of Clinical Endocrinologist (AACE) suggests more intensive criteria for statin therapy initiation in diabetic patients (LDL-C < 55 mg/dL, Non-HDL (HDL-C subtracted from total cholesterol) < 80 mg/dL, and apoB < 70 mg/dL) with high risk factors including advanced ASCVD after LDL-C < 70 mg/dL achievement, confirmed clinical CVD in diabetic patients, chronic kidney disease (CKD) 3-4 or heterozygous familial hypercholesterolemia, and premature ASCVD background (< 55 and < 65 for males and females, respectively).[64]

Better response to statin therapy has also been observed in diabetic patients aged 40-75 years; while, this effect was not observed in patients > 75 years. This may be due to low number recruitment of older patients in primary prevention trials.[65] Therefore, in patients ≥ 75 years a moderate dose of statins is recommended. Although, a continuous monitoring is required for the risk-benefit assessment to decrease the statins dose if required.[65]

Overall, patient on statin-based treatment need their serum LDL-C level to be measured every 4-12 weeks after the statin prescribing initiation. If a patient showed any

Table 3. Statin therapy recommendations regarding the ASCVD score and serum LDL concentration in diabetic patients

LDL-C level (mg/dL)	ASCVD risk (%)	Age (y)	Statin therapy
<70	<7.5	Any age	NR
>70	<7.5	40-75	Moderate Intensity (rosuvastatin 5–10 mg/d, simvastatin 20–40 mg/d, pravastatin 40–80 mg/d, lovastatin 40 mg/d, fluvastatin XL 80 mg/d, pitavastatin 2–4 mg/d)
<70	≥7.5	40-75	High Intensity (atorvastatin 40–80 mg/d, rosuvastatin 20–40 mg/d)

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein-cholesterol; NR; not required.

drug-associated side effects, another dose or an alternative statin should be tried.[61]

Moderate dose statin-based treatment decreases LDL-C by 30%-45%. This strategy includes atorvastatin 10–20 mg/d, rosuvastatin 5–10 mg/d, simvastatin 20–40 mg/d, pravastatin 40–80 mg/d, lovastatin 40 mg/d, fluvastatin XL 80 mg/d, or pitavastatin 2–4 mg/d. In contrast, high dose statin-based treatment leads to LDL-C decrease more than 50% and includes atorvastatin 40–80 mg/d or rosuvastatin 20–40 mg/d. Generally, low dose statin-based treatment is not a therapeutic choice for diabetic patients; however, it sometimes is the only tolerable dose by the patient.[62]

Statins side effects

Musculoskeletal system

Almost, all statins are correlated with musculoskeletal complications, so that myalgia and myositis are the most and the least intensive symptoms, respectively, with a significant serum creatine kinase (CK) level increase.[66] Rhabdomyolysis is the most severe musculoskeletal disorder with a 10 fold increase of CK higher than the normal range. Upper level of CK is also associated with myoglobinuria, renal disorder and serum electrolytes imbalance.[66] Overall, the rate of statin-related musculoskeletal side effects is very low.[66,67] Various studies have also reported different myopathy rates ranging 0.1-10%; probably, due to different definitions, various data collection methods and high rate of reporting bias.[17] Khan et al[67] in a study on 10 000 patients receiving statins in the United States reported the myalgia as the most prevalent cause of statin therapy cease in more than 60% of the patients. Additionally, a Cochrane review including 9 clinical trials also reported that 3551 participants out of 37939 patients (9.4%) exhibited myalgia symptoms and demonstrated no evidence regarding the increased risk with the pooled estimate of 1.03 (95% CI, 0.97-1.06). However, rhabdomyolysis was observed in only 3 out of 19 410 patients in a total of 6 trials.[68]

Heart Protection study in a research on 20 000 patients receiving simvastatin or placebo, reported the annual risk of myopathy as 0.01%. Moreover, five and three patients in simvastatin and placebo groups showed rhabdomyolysis symptoms, respectively. 49 patients (0.5%) in simvastatin group and 50 patients (0.5%) in the placebo group also ceased the drug use due to the side effects.[5] Large Cholesterol Treatment Trialist study also reported the overall rate of rhabdomyolysis as 1/10 000 patients in both statin and control groups. In this study, more intensive statin group showed an increased rhabdomyolysis risk compared to the less intensive counterparts.[17] LIVES study also showed one rhabdomyolysis case and one muscle weakness among 20 000 patients on pitavastatin. The overall frequency of side effects in this study was 10.4%; however, the number of patients with myalgia and other musculoskeletal complications was not reported.[69]

Overall, all major statin therapy trials, including massive meta-analysis studies have declared a rare severe musculoskeletal complications of statins, and generally, the benefits of statin therapy overweigh their small musculoskeletal-related side effects.[17]

Liver

In 1-3% of patients on statin therapy, elevated hepatic transaminases have been observed.[70] This is usually dose dependent and occurs during the first trimester from the therapy initiation. However, this condition was not associated with the chronic liver dysfunction.[70] Russo et al in a study on 1188 patients on statins found 22 patients with drug-induced hepatic injury. The majority of these patients were females (68%) with various drug use periods from 34 days to 10 years (median 155 days). Four patients also proceeded to chronic (mainly autoimmune phenotype) hepatic disease.[70]

A Cochrane review including 18 clinical trial studies evaluating the effects of statin therapy for primary prevention of CVD, reported a weak correlation between the increased level of hepatic enzymes and the statins use.[68] Similar results were also reported by another large meta-analysis study including 35 statin therapy trials.[71]

The clinical significance of this "transaminitis" is debatable; because, many of these patients are asymptomatic regarding the statin therapy-induced hepatic disorders.[17] Additionally, liver failure cases due to statin use are very rare.[17] Although, the baseline evaluation of liver function may be useful, its routine monitoring is not recommended. Patient with mild elevated liver function tests can also stay on statin therapy by close monitoring.[17]

Diabetes mellitus

Recent evidences indicate that statins may enhance the risk of diabetes mellitus because of their inhibitory effect on insulin signaling pathway, affecting pancreas beta cells and insulin resistance induction.[72,73] Wang et al[74] in a study reported that 30-40% decrease in LDL-C level after statins use increases the risk of T2DM by at least 13% and this risk is increased to 29% when the LDL-C level is reduced by 40-50%. Satter et al[75] in a meta-analysis study including13 clinical trial study also showed a 9% increase in new onset diabetes mellitus after 4 years of follow-up. Preiss et al[76] meta-analysis including 5 large clinical trial studies with 32752 patients also reported an increased rate of diabetes mellitus in patients receiving statins intensive dose compared to moderate dose. Furthermore, elevated insulin resistance was observed in non-dyslipidemia Asian patients after statin therapy.[77]

Despite the above mentioned findings, not all statins are diabetogenic.[17] For example, LIVES study on 1197 patients with diabetes mellitus and hypercholesterolemia showed that pitavastatin prescribing does not affect the glucose metabolism; however, one patients experienced

new onset diabetes during the follow-up.[69] Moreover, a significant 0.28% decrease in HbA1C was observed in diabetic patients under the treatment.[69]

Two main mechanisms have been proposed for diabetogenic effects of statins: (i) hepatic endogenous glucose production (EGP) and ii) effect on pancreas beta cells.[78] In the former mechanism, statins activate the pregnane X receptor (PXR) in the cytoplasm of human hepatic cells.[79] PXR in combination with serum/glucocorticoid regulated kinase 2 (SGK2) induce the dephosphorylation of protein phosphatase 2CA (PP2CA).[79] PXR and dephosphorylated SGK2 are then translocated to the nucleus and by retinoid X receptor (RXR) bind to PXR-SGK2 response element (PSRE) and insulin response sequence region (IRS), leading to the activation of phosphoenolpyruvate carboxykinase 1 (PEPCK1) and glucose 6 phosphatase (G6Pase) and consequently EGP activation.[79] PEPCK1 and G6Pase are also alternatively activated through autophagy flux by the intermediary effect of MAP1LC3A. Autophagy is a regulated cellular destructive process which is overactivated during starvation, ER and intracellular stress[80] (Figure 3).

In the latter hypothetical mechanism demonstrated in mouse MIN6 and rat INS1 beta cells, LDL-C receptor is upregulated in pancreas beta cells after HMG-CoA reductase inhibition by statins, leading to increased LDL-C uptake.[81] The elevated intracellular LDL-C level interferes with glucokinase translocation into the mitochondria, as well as ATP-binding cassette transporter ABCA1 activity.[82] The impaired ABCA1 activity has been associated with the decreased insulin secretion from pancreas beta cells.[83] Accordingly, the decreased expression of glucose transporter 2 (Glut2) causes intracellular ATP fall, inhibition of ATP-dependent potassium channel closure, membrane depolarization, diminished influx of calcium, and intracellular calcium level fall, all of which lead to the decreased insulin secretion.[84]

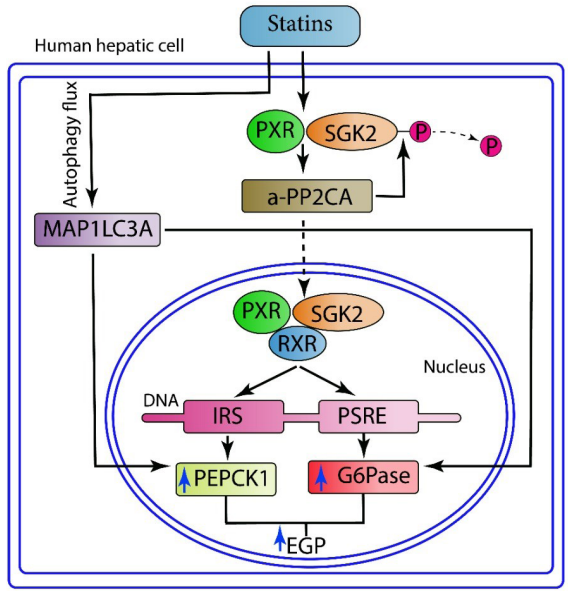

Figure 3. Diabetogenic activity of statins in human hepatic cells. Statins can increase EGP through PXR-SGK2 complex or autophagy flux. PXR: pregnane X receptor; Serum/glucocorticoid regulated kinase 2 (SGK2); PP2CA: protein phosphatase 2CA; RXR: retinoid X receptor; PSRE: PXR-SGK2 response elements; IRS: insulin response sequence

Moreover, Statins can also inhibit glucagon-like peptide 1 (GLP1) which in turn inactivates adenylate cyclase, leading to decreased intracellular cyclic AMP (cAMP), decreased activity of protein kinase A (PKA) and exchange protein directly activated by cAMP 2 (EPAC2) and finally decreased insulin excretion.[84] Inhibitory effect of statins on G-protein-coupled receptor 40 (GPR40) as a receptor for long chain fatty acids also can decrease the insulin secretion by lowering the intracellular calcium concentration.[84] Finally, synthesis inhibition of FPP by statins may also inactivate the Ras/Raf/ERK/CREB cascade resulting in the decreased insulin gene promoter activity and consequently decreased insulin secretion[85] (Figure 4).

Although there are evidences indicating the diabetogenic properties of some statins, diabetic patients are the main group which benefit the statin therapy against cardiovascular risks.[17] Additionally, there are no convincing evidences indicating the deteriorating effects of statins on glycemic control.[17]

Kidney

Rhabdomyolysis due to statin therapy can induce tubular obstruction, leading to tubular injury and ischemia.[86] Statin therapy can also be correlated with benign proteinuria because of the inhibition of tubular reabsorption of low molecular weight proteins.[86] However, the clinical importance of this type of proteinuria remains unclear, as the excreted proteins in this condition differs from other glomerular diseases.[86] Additionally, there is no evidence indicating the chronic renal dysfunction following statin therapy.[17]

A meta-analysis study by Sandhu et al[87] analyzing 39 000 patients showed a significant decrease in glomerular filtration rate (GFR) in patients with CVD compared to controls after the statin therapy; however, no significant differences were observed between diabetic patients and patients with the hypertensive kidney diseases. In contrast, the LIVES study reported an increased eGFR at the end of follow up period after pitavastatin prescribing.[69] Bianchi et al[88] in their study also reported a decreased proteinuria following atorvastatin addition to angiotensin converting enzyme inhibitor. Recent trials including PREVENDIT,[89] ESPLANADE[90] and PLANET[91] also reported no decreased proteinuria after statin therapy.

The main concern regarding the statin therapy is related to acute kidney injury.[92] Dormuth et al[93] in a large retrospective observational study on more than 2 million and another 59,636 patients receiving statins without or

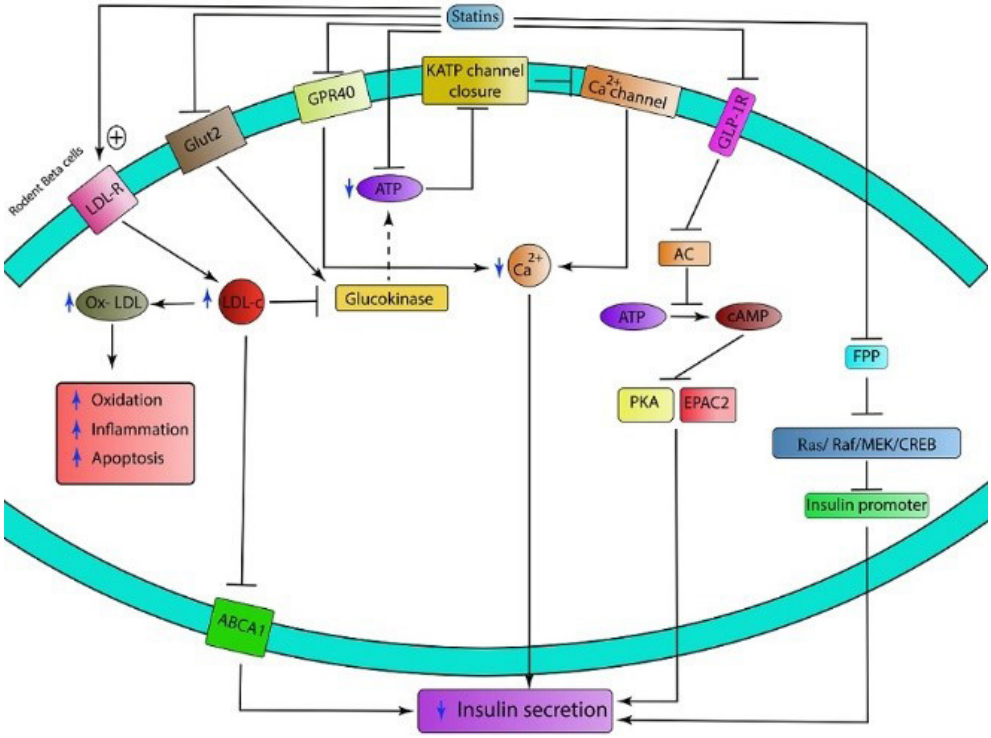

Figure 4. Hypothetical inhibitory effects of statins on insulin secretion in rodent beta cells. LDL-R: low density lipoprotein receptor; Glut 2: glucose transferase 2; GPR40: G-protein-coupled receptor 40; GLP-1R: glucagon-like peptide-1 receptor; ox-LDL: oxidized LDL; AC: adenylate cyclase; ABCA1: ATP-binding cassette transporter A1; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; EPAC2: exchange protein directly activated by cAMP 2; FPP: farnesyl pyrophosphate

with prior history of CKD, respectively, reported 4691 (0.2%) and 1896 (3%) hospitalizations for acute kidney injury (AKI) in mentioned groups within 4 months after statin therapy. Moreover, the hospitalization rate due to AKI was 34% higher in patients with no prior kidney disease receiving high intensity statins compared to low intensity regimens.[93]

On the other side, a large number of patients receiving statins suffer from underlying CKD as a strong predictor for CVD.[17] Large 4-D38 and AURORA39 trials showed no current significant evidence regarding the protective role of statins for patients on dialysis.[94,95] However, it has been revealed that statins improve the cardiovascular outcomes in dialysis-independent patients.[96]

Discussion

The LDL-c and cholesterol lowering properties of statins via HMG-CoA reductase inhibition has been previously well documented.[97] Studies have revealed that statins (especially atorvastatin) also significantly decrease the TG level by 10-20%.[98] Additionally, the statins effect on inflammation and coagulation factors has also been studied [36]. One study has reported a significant lowered CRP level in patients on statin.[99] Atorvastatin has also decreased the hs-CRP level in diabetic or non-diabetic patients.[100] The proposed mechanism for this effect has been described via IL-1b-inducible CRP decrease in hepatocytes.[100,101] IL-6 is probably implicated in insulin signaling in adipose tissue, liver, and muscle cells.[102] On the other side, IL-1β as a pro-inflammatory cytokine prevents the function of β-cells and induces their apoptosis.[102] Moreover, the anti-inflammatory effects of statins can be due to lipid and lipid derivatives decrease such as lysolecithin, platelet activating factor, and oxysterols which are known as pre-inflammatory factors.[103]

Regarding the homocysteine, controversial findings have been reported.[36] For instance, Miltiadous et al[104] reported no significant effect on homocysteine level after 40 mg/d atorvastatin prescription for 10 weeks. Milionis et al[105] also reported no significant change in homocysteine level in diabetic patients on hemodialysis; however, a significant improvement in lipid profile and hs-CRP level were observed after atorvastatin administration. In contrast, van der Loo et al[106] showed a significant increase in homocysteine following 80 mg/d atorvastatin prescription in patients with peripheral arterial disease. These controversial results may be due to different statin doses, duration of intervention, study on different diseases and patient's metabolic profile.

Fibrinogen is an acute-phase reactant with a crucial role in thrombogenesis, inflammation, immune responses and atherogenesis.[107] It is well-documented that statins decrease the fibrinogen level and also increases endothelial nitric oxide synthesis.[108]

Although, statins use has widely been accepted in medical communities, they may exert some side effects on glucose level and liver enzymes.[109] Statins probably inhibit 3T3-L1 pre-adipocytes differentiation and suppress the

GLUT4 expression, leading to impaired glucose uptake in adipocytes.[110] These finding indicate the fact that statins should be administered more carefully regarding the patient's disease stage and metabolic status.

Conclusion

Despite the beneficial effects of statins in blood cholesterol lowering, mortality decrease due to CVD and stroke in patients with developed atherosclerosis, and dyslipidemia improvement, their other effects, including anti-inflammatory effects, inflammatory cytokines and hs-CRP decrease, and anti-coagulation properties such as anti-thrombogenic effects and decrease of inflammatory factors (fibrinogen, vWF, V and X) production have not well studied, especially in T2DM. These effects will be considerable following intensive dosed prescribing of statins compared to moderate or low doses, and should be considered as an important issue in T2DM control.

Acknowledgments

Authors would acknowledge the Endocrine Research Center for their great help.

Authors' Contribution

Conceptualization: Mitra Niafar and Vahideh Sadra.
Funding acquisition: Mitra Niafar.
Methodology: Amir Mehdizadeh.
Project administration: Amir Mehdizadeh.
Software: Vahid Hosseini.
Supervision: Amir Mehdizadeh.
Writing–original draft: Vahideh Sadra.
Writing–review & editing: Amir Mehdizadeh.

Competing Interests

Authors declare no conflict of interests.

Ethical Approval

This study was approved by the Ethics Committee of Human Research at Tabriz University of Medical Sciences with code Ir.tums.rec.1393168.

Funding

This work was done as a sub-specialty dissertation for Dr.Vahideh Sadra (Grant No.:93/5-7/18).

References

1. Palazhy S, Viswanathan V. Lipid abnormalities in type 2 diabetes mellitus patients with overt nephropathy. Diabetes Metab J. 2017;41(2):128-34. doi: 10.4093/dmj.2017.41.2.128.
2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459-72. doi: 10.1093/eurheartj/ehx144.
3. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes dyslipidemia. Diabetes Ther. 2016;7(2):203-19. doi: 10.1007/s13300-016-0167-x.
4. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-96. doi: 10.1016/s0140-6736(04)16895-5.
5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22. doi: 10.1016/s0140-6736(02)09327-3.
6. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007;45(4):645-54; discussion 53-4. doi: 10.1016/j.jvs.2006.12.054.
7. Corsonello A, Garasto S, Abbatecola AM, Rose G, Passarino G, Mazzei B, et al. Targeting inflammation to slow or delay functional decline: where are we? Biogerontology. 2010;11(5):603-14. doi: 10.1007/s10522-010-9289-0.
8. Proksch E, Elias PM, Feingold KR. Regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity in murine epidermis. Modulation of enzyme content and activation state by barrier requirements. J Clin Invest. 1990;85(3):874-82. doi: 10.1172/jci114514.
9. Singh P, Kohr D, Kaps M, Blaes F. Influence of statins on MHC class I expression. Ann N Y Acad Sci. 2009;1173:746-51. doi: 10.1111/j.1749-6632.2009.04646.x.
10. Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. Arterioscler Thromb Vasc Biol. 2005;25(2):287-94. doi: 10.1161/01.ATV.0000151647.14923.ec.
11. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol Ther. 1999;84(3):413-28. doi: 10.1016/s0163-7258(99)00045-5.
12. Sehayek E, Butbul E, Avner R, Levkovitz H, Eisenberg S. Enhanced cellular metabolism of very low density lipoprotein by simvastatin. A novel mechanism of action of HMG-CoA reductase inhibitors. Eur J Clin Invest. 1994;24(3):173-8. doi: 10.1111/j.1365-2362.1994.tb00984.x.
13. Ginsberg HN, Le NA, Short MP, Ramakrishnan R, Desnick RJ. Suppression of apolipoprotein B production during treatment of cholesteryl ester storage disease with lovastatin. Implications for regulation of apolipoprotein B synthesis. J Clin Invest. 1987;80(6):1692-7. doi: 10.1172/jci113259.
14. Gaw A, Packard CJ, Murray EF, Lindsay GM, Griffin BA, Caslake MJ, et al. Effects of simvastatin on apoB metabolism and LDL subfraction distribution. Arterioscler Thromb. 1993;13(2):170-89. doi: 10.1161/01.atv.13.2.170.
15. Kostner GM, Gavish D, Leopold B, Bolzano K, Weintraub MS, Breslow JL. HMG CoA reductase inhibitors lower LDL cholesterol without reducing Lp(a) levels. Circulation. 1989;80(5):1313-9. doi: 10.1161/01.cir.80.5.1313.
16. Blum CB. Comparison of properties of four inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Am J Cardiol. 1994;73(14):3d-11d. doi: 10.1016/0002-9149(94)90626-2.
17. Ramkumar S, Raghunath A, Raghunath S. Statin therapy: review of safety and potential side effects. Acta Cardiol Sin. 2016;32(6):631-9. doi: 10.6515/acs20160611a.
18. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences. Clin Pharmacokinet. 1997;32(5):403-25. doi: 10.2165/00003088-199732050-00005.
19. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med. 2001;5(4):378-87. doi: 10.1111/j.1582-4934.2001.tb00172.x.
20. Blumenthal RS. Statins: effective antiatherosclerotic therapy. Am Heart J. 2000;139(4):577-83. doi: 10.1016/s0002-

8703(00)90033-4.
21. Bernini F, Didoni G, Bonfadini G, Bellosta S, Fumagalli R. Requirement for mevalonate in acetylated LDL induction of cholesterol esterification in macrophages. Atherosclerosis. 1993;104(1-2):19-26. doi: 10.1016/0021-9150(93)90172-q.
22. Sillars A, Sattar N. Management of lipid abnormalities in patients with diabetes. Curr Cardiol Rep. 2019;21(11):147. doi: 10.1007/s11886-019-1246-1.
23. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78. doi: 10.1016/s0140-6736(05)67394-1.
24. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81. doi: 10.1016/s0140-6736(10)61350-5.
25. Newman CB, Preiss D, Tobert JA, Jacobson TA, Page RL 2nd, Goldstein LB, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2019;39(2):e38-e81. doi: 10.1161/atv.0000000000000073.
26. Branchi A, Fiorenza AM, Torri A, Muzio F, Rovellini A, Berra C, et al. Effects of atorvastatin 10 mg and simvastatin 20 mg on serum triglyceride levels in patients with hypercholesterolemia. Curr Ther Res Clin Exp. 2001;62(5):408-15. doi: 10.1016/s0011-393x(01)89005-6.
27. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, et al. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol. 2019;14(1):50-9. doi: 10.15420/ecr.2018.33.1.
28. Williamson RT. On the treatment of glycosuria and diabetes mellitus with sodium salicylate. Br Med J. 1901;1(2100):760-2. doi: 10.1136/bmj.1.2100.760.
29. Reid J, Macdougall AI, Andrews MM. Aspirin and diabetes mellitus. Br Med J. 1957;2(5053):1071-4. doi: 10.1136/bmj.2.5053.1071.
30. Shulman GI. Unraveling the cellular mechanism of insulin resistance in humans: new insights from magnetic resonance spectroscopy. Physiology (Bethesda). 2004;19:183-90. doi: 10.1152/physiol.00007.2004.
31. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87-91. doi: 10.1126/science.7678183.
32. Ogston D, McAndrew GM. Fibrinolysis in obesity. Lancet. 1964;2(7371):1205-7. doi: 10.1016/s0140-6736(64)91042-6.
33. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132-40. doi: 10.1016/s0140-6736(09)61717-7.
34. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes. 2003;52(7):1799-805. doi: 10.2337/diabetes.52.7.1799.
35. Muhlestein JB, May HT, Jensen JR, Horne BD, Lanman RB, Lavasani F, et al. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. J Am Coll Cardiol. 2006;48(2):396-401. doi: 10.1016/j.jacc.2006.05.009.
36. Niafar M, Bahrami A, Lotfi Yagin N, Najafipour F, Aghamohammadzadeh N, Sadra V. Effect of high dose versus low dose of atorvastatin therapy on inflammation and coagulation factors in type 2 diabetic patients; a randomized clinical trial study. Immunopathol Persa. 2019;5(1):e01. doi: 10.15171/ipp.2019.01.
37. Tan KC, Chow WS, Tam SC, Ai VH, Lam CH, Lam KS. Atorvastatin lowers C-reactive protein and improves endothelium-dependent vasodilation in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2002;87(2):563-8. doi: 10.1210/jcem.87.2.8249.
38. van de Ree MA, Huisman MV, Princen HM, Meinders AE, Kluft C. Strong decrease of high sensitivity C-reactive protein with high-dose atorvastatin in patients with type 2 diabetes mellitus. Atherosclerosis. 2003;166(1):129-35. doi: 10.1016/s0021-9150(02)00316-7.
39. Sobczak AIS, Stewart AJ. Coagulatory defects in type-1 and type-2 diabetes. Int J Mol Sci. 2019;20(24):6345. doi: 10.3390/ijms20246345.
40. Verkleij CJ, de Bruijn RE, Meesters EW, Gerdes VE, Meijers JC, Marx PF. The hemostatic system in patients with type 2 diabetes with and without cardiovascular disease. Clin Appl Thromb Hemost. 2011;17(6):E57-63. doi: 10.1177/1076029610384112.
41. Rothschild AM, Reis ML, Melo VL, Foss MC, Gallo L Jr. Increased kininogen levels observed in plasma of diabetic patients are corrected by the administration of insulin. Horm Metab Res. 1999;31(5):326-8. doi: 10.1055/s-2007-978746.
42. El-Hagracy RS, Kamal GM, Sabry IM, Saad AA, Abou El Ezz NF, Nasr HA. Tissue factor, tissue factor pathway inhibitor and factor VII activity in cardiovascular complicated type 2 diabetes mellitus. Oman Med J. 2010;25(3):173-8. doi: 10.5001/omj.2010.52.
43. Kim HK, Kim JE, Park SH, Kim YI, Nam-Goong IS, Kim ES. High coagulation factor levels and low protein C levels contribute to enhanced thrombin generation in patients with diabetes who do not have macrovascular complications. J Diabetes Complications. 2014;28(3):365-9. doi: 10.1016/j.jdiacomp.2014.01.006.
44. Barillari G, Fabbro E, Pasca S, Bigotto E. Coagulation and oxidative stress plasmatic levels in a type 2 diabetes population. Blood Coagul Fibrinolysis. 2009;20(4):290-6. doi: 10.1097/MBC.0b013e328329e49b.
45. Song DY, Gu JY, Yoo HJ, Kim YI, Nam-Goong IS, Kim ES, et al. Activation of factor XII and kallikrein-kinin system combined with neutrophil extracellular trap formation in diabetic retinopathy. Exp Clin Endocrinol Diabetes. 2021;129(8):560-5. doi: 10.1055/a-0981-6023.
46. Mansfield MW, Kohler HP, Ariëns RA, McCormack LJ, Grant PJ. Circulating levels of coagulation factor XIII in subjects with type 2 diabetes and in their first-degree relatives. Diabetes Care. 2000;23(5):703-5. doi: 10.2337/diacare.23.5.703.
47. Madan R, Gupt B, Saluja S, Kansra UC, Tripathi BK, Guliani BP. Coagulation profile in diabetes and its association with diabetic microvascular complications. J Assoc Physicians India. 2010;58:481-4.
48. Addai-Mensah O, Annani-Akollor ME, Nsafoah FO, Fondjo LA, Owiredu EW, Danquah KO, et al. Effect of poor glycaemic control on plasma levels and activity of protein C, protein S, and antithrombin III in type 2 diabetes mellitus. PLoS One. 2019;14(9):e0223171. doi: 10.1371/journal.pone.0223171.
49. Aslan B, Eren N, Ciğerli Ş, Müldür F, Yücel N. Evaluation of plasma protein C antigen, protein C activity and thrombomodulin levels in type 2 diabetic patients. Turk J Med Sci. 2005;35(5):305-10.
50. Yasuma T, Yano Y, D'Alessandro-Gabazza CN, Toda M, Gil-Bernabe P, Kobayashi T, et al. Amelioration of diabetes by protein S. Diabetes. 2016;65(7):1940-51. doi: 10.2337/db15-1404.
51. Sommeijer DW, Hansen HR, van Oerle R, Hamulyak K, van

Zanten AP, Meesters E, et al. Soluble tissue factor is a candidate marker for progression of microvascular disease in patients with Type 2 diabetes. J Thromb Haemost. 2006;4(3):574-80. doi: 10.1111/j.1538-7836.2005.01763.x.
52. Fattah MA, Shaheen MH, Mahfouz MH. Disturbances of haemostasis in diabetes mellitus. Dis Markers. 2003;19(6):251-8. doi: 10.1155/2004/797458.
53. Hori Y, Gabazza EC, Yano Y, Katsuki A, Suzuki K, Adachi Y, et al. Insulin resistance is associated with increased circulating level of thrombin-activatable fibrinolysis inhibitor in type 2 diabetic patients. J Clin Endocrinol Metab. 2002;87(2):660-5. doi: 10.1210/jcem.87.2.8214.
54. Yoshino S, Fujimoto K, Takada T, Kawamura S, Ogawa J, Kamata Y, et al. Molecular form and concentration of serum α2-macroglobulin in diabetes. Sci Rep. 2019;9(1):12927. doi: 10.1038/s41598-019-49144-7.
55. Rubba P. Effects of atorvastatin on the different phases of atherogenesis. Drugs. 2007;67 Suppl 1:17-27. doi: 10.2165/00003495-200767001-00003.
56. Ludwig S, Shen GX. Statins for diabetic cardiovascular complications. Curr Vasc Pharmacol. 2006;4(3):245-51. doi: 10.2174/157016106777698388.
57. Ferroni P, Della-Morte D, Pileggi A, Valente MG, Martini F, La Farina F, et al. Impact of statins on the coagulation status of type 2 diabetes patients evaluated by a novel thrombin-generation assay. Cardiovasc Drugs Ther. 2012;26(4):301-9. doi: 10.1007/s10557-012-6388-y.
58. Park HS, Gu JY, Yoo HJ, Han SE, Park CH, Kim YI, et al. Thrombin generation assay detects moderate-intensity statin-induced reduction of hypercoagulability in diabetes. Clin Appl Thromb Hemost. 2018;24(7):1095-101. doi: 10.1177/1076029618766254.
59. Sommeijer DW, MacGillavry MR, Meijers JC, Van Zanten AP, Reitsma PH, Ten Cate H. Anti-inflammatory and anticoagulant effects of pravastatin in patients with type 2 diabetes. Diabetes Care. 2004;27(2):468-73. doi: 10.2337/diacare.27.2.468.
60. Macchia A, Laffaye N, Comignani PD, Cornejo Pucci E, Igarzabal C, Scazziota AS, et al. Statins but not aspirin reduce thrombotic risk assessed by thrombin generation in diabetic patients without cardiovascular events: the RATIONAL trial. PLoS One. 2012;7(3):e32894. doi: 10.1371/journal.pone.0032894.
61. American Diabetes Association. 9. Cardiovascular disease and risk management: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S86-S104. doi: 10.2337/dc18-S009.
62. Khalil S, Khayyat S, Al-Khadra Y, Alraies MC. Should all diabetic patients take statin therapy regardless of serum cholesterol level? Expert Rev Cardiovasc Ther. 2019;17(4):237-9. doi: 10.1080/14779072.2019.1590198.
63. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-25. doi: 10.1016/s0140-6736(08)60104-x.
64. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract. 2017;23(Suppl 2):1-87. doi: 10.4158/ep171764.appgl.
65. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005-16. doi: 10.1016/s0140-6736(03)13636-7.
66. Pedro-Botet J, Núñez-Cortés JM, Flores JA, Rius J. Muscle symptoms related with statin therapy in general practice. Atherosclerosis. 2015;241(1):e197. doi: 10.1016/j.atherosclerosis.2015.04.957.
67. Khan A, Maki KC, Ito MK, Cohen JD, Sponseller CA, Bell M, et al. Statin associated muscle symptoms: characteristics of patients and recommendations by providers. J Clin Lipidol. 2015;9(3):460. doi: 10.1016/j.jacl.2015.03.080.
68. Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2011(1):CD004816. doi: 10.1002/14651858.CD004816.pub4.
69. Yokote K, Shimano H, Urashima M, Teramoto T. Efficacy and safety of pitavastatin in Japanese patients with hypercholesterolemia: LIVES study and subanalysis. Expert Rev Cardiovasc Ther. 2011;9(5):555-62. doi: 10.1586/erc.11.47.
70. Russo MW, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE, et al. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. Hepatology. 2014;60(2):679-86. doi: 10.1002/hep.27157.
71. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006;114(25):2788-97. doi: 10.1161/circulationaha.106.624890.
72. Bang CN, Okin PM. Statin treatment, new-onset diabetes, and other adverse effects: a systematic review. Curr Cardiol Rep. 2014;16(3):461. doi: 10.1007/s11886-013-0461-4.
73. 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):1109-17. doi: 10.1007/s00125-015-3528-5.
74. Wang S, Cai R, Yuan Y, Varghese Z, Moorhead J, Ruan XZ. Association between reductions in low-density lipoprotein cholesterol with statin therapy and the risk of new-onset diabetes: a meta-analysis. Sci Rep. 2017;7:39982. doi: 10.1038/srep39982.
75. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735-42. doi: 10.1016/s0140-6736(09)61965-6.
76. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. Jama. 2011;305(24):2556-64. doi: 10.1001/jama.2011.860.
77. Hyun M, Choi BG, Seo HS, Lee E, Choi SY, Xu S, et al. Risk of increased insulin resistance with statin therapy for non-dyslipidemic asians. Atherosclerosis. 2015;241(1):e196-e7. doi: 10.1016/j.atherosclerosis.2015.04.954.
78. van Stee MF, de Graaf AA, Groen AK. Actions of metformin and statins on lipid and glucose metabolism and possible benefit of combination therapy. Cardiovasc Diabetol. 2018;17(1):94. doi: 10.1186/s12933-018-0738-4.
79. Gotoh S, Negishi M. Statin-activated nuclear receptor PXR promotes SGK2 dephosphorylation by scaffolding PP2C to induce hepatic gluconeogenesis. Sci Rep. 2015;5:14076. doi: 10.1038/srep14076.
80. He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet. 2009;43:67-93. doi: 10.1146/annurev-genet-102808-114910.
81. Ruscica M, Macchi C, Morlotti B, Sirtori CR, Magni P. Statin therapy and related risk of new-onset type 2 diabetes

mellitus. Eur J Intern Med. 2014;25(5):401-6. doi: 10.1016/j.ejim.2014.03.003.
82. Hao M, Head WS, Gunawardana SC, Hasty AH, Piston DW. Direct effect of cholesterol on insulin secretion: a novel mechanism for pancreatic beta-cell dysfunction. Diabetes. 2007;56(9):2328-38. doi: 10.2337/db07-0056.
83. Vergeer M, Brunham LR, Koetsveld J, Kruit JK, Verchere CB, Kastelein JJ, et al. Carriers of loss-of-function mutations in ABCA1 display pancreatic beta-cell dysfunction. Diabetes Care. 2010;33(4):869-74. doi: 10.2337/dc09-1562.
84. Yaluri N, Modi S, López Rodríguez M, Stančáková A, Kuusisto J, Kokkola T, et al. Simvastatin impairs insulin secretion by multiple mechanisms in MIN6 cells. PLoS One. 2015;10(11):e0142902. doi: 10.1371/journal.pone.0142902.
85. Sun H, Li Y, Sun B, Hou N, Yang J, Zheng M, et al. Atorvastatin inhibits insulin synthesis by inhibiting the Ras/Raf/ERK/CREB pathway in INS-1 cells. Medicine (Baltimore). 2016;95(39):e4906. doi: 10.1097/md.0000000000004906.
86. Brown WV. Safety of statins. Curr Opin Lipidol. 2008;19(6):558-62. doi: 10.1097/MOL.0b013e328319baba.
87. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol. 2006;17(7):2006-16. doi: 10.1681/asn.2006010012.
88. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. Am J Kidney Dis. 2003;41(3):565-70. doi: 10.1053/ajkd.2003.50140.
89. Atthobari J, Brantsma AH, Gansevoort RT, Visser ST, Asselbergs FW, van Gilst WH, et al. The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and an observational cohort study. Nephrol Dial Transplant. 2006;21(11):3106-14. doi: 10.1093/ndt/gfl244.
90. Ruggenenti P, Perna A, Tonelli M, Loriga G, Motterlini N, Rubis N, et al. Effects of add-on fluvastatin therapy in patients with chronic proteinuric nephropathy on dual renin-angiotensin system blockade: the ESPLANADE trial. Clin J Am Soc Nephrol. 2010;5(11):1928-38. doi: 10.2215/cjn.03380410.
91. de Zeeuw D, Anzalone DA, Cain VA, Cressman MD, Heerspink HJ, Molitoris BA, et al. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. Lancet Diabetes Endocrinol. 2015;3(3):181-90. doi: 10.1016/s2213-8587(14)70246-3.
92. Bangalore S, Fayyad R, Hovingh GK, Laskey R, Vogt L, DeMicco DA, et al. Statin and the risk of renal-related serious adverse events: analysis from the IDEAL, TNT, CARDS, ASPEN, SPARCL, and other placebo-controlled trials. Am J Cardiol. 2014;113(12):2018-20. doi: 10.1016/j.amjcard.2014.03.046.
93. Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, Raymond CB, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. BMJ. 2013;346:f880. doi: 10.1136/bmj.f880.
94. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238-48. doi: 10.1056/NEJMoa043545.
95. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395-407. doi: 10.1056/NEJMoa0810177.
96. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181-92. doi: 10.1016/s0140-6736(11)60739-3.
97. Tsikas D, Pham VV, Suchy MT, van de Ree MA, Huisman MV, Frölich JC, et al. No effects of atorvastatin (10 mg/d or 80 mg/d) on nitric oxide, prostacyclin, thromboxane and oxidative stress in type 2 diabetes mellitus patients of the DALI study. Pharmacol Res. 2015;94:1-8. doi: 10.1016/j.phrs.2015.01.004.
98. Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridemia. Am J Cardiol. 1998;81(4a):66b-9b. doi: 10.1016/s0002-9149(98)00041-1.
99. Lyngdoh T, Vollenweider P, Waeber G, Marques-Vidal P. Association of statins with inflammatory cytokines: a population-based Colaus study. Atherosclerosis. 2011;219(1):253-8. doi: 10.1016/j.atherosclerosis.2011.07.117.
100. Gensini GF, Gori AM, Dilaghi B, Rostagno C, Gaw A, Blanco-Colio LM, et al. Effect of atorvastatin on circulating hsCRP concentrations: a sub-study of the achieve cholesterol targets fast with atorvastatin stratified titration (ACTFAST) study. Int J Cardiol. 2010;142(3):257-64. doi: 10.1016/j.ijcard.2008.12.213.
101. Arnaud C, Burger F, Steffens S, Veillard NR, Nguyen TH, Trono D, et al. Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins. Arterioscler Thromb Vasc Biol. 2005;25(6):1231-6. doi: 10.1161/01.ATV.0000163840.63685.0c.
102. Donath MY, Schumann DM, Faulenbach M, Ellingsgaard H, Perren A, Ehses JA. Islet inflammation in type 2 diabetes: from metabolic stress to therapy. Diabetes Care. 2008;31 Suppl 2:S161-4. doi: 10.2337/dc08-s243.
103. Liu Y, Hultén LM, Wiklund O. Macrophages isolated from human atherosclerotic plaques produce IL-8, and oxysterols may have a regulatory function for IL-8 production. Arterioscler Thromb Vasc Biol. 1997;17(2):317-23. doi: 10.1161/01.atv.17.2.317.
104. Miltiadous G, Papakostas J, Chasiotis G, Seferiadis K, Elisaf M. Statins and homocysteine. Atherosclerosis. 2003;166(1):199-200. doi: 10.1016/s0021-9150(02)00318-0.
105. Milionis HJ, Papakostas J, Kakafika A, Chasiotis G, Seferiadis K, Elisaf MS. Comparative effects of atorvastatin, simvastatin, and fenofibrate on serum homocysteine levels in patients with primary hyperlipidemia. J Clin Pharmacol. 2003;43(8):825-30. doi: 10.1177/0091270003255920.
106. van der Loo B, Spring S, Koppensteiner R. High-dose atorvastatin treatment in patients with peripheral arterial disease: effects on platelet aggregation, blood rheology and plasma homocysteine. Clin Hemorheol Microcirc. 2011;47(4):241-51. doi: 10.3233/ch-2011-1386.
107. Min L, Shao S, Wu X, Cong L, Liu P, Zhao H, et al. Anti-inflammatory and anti-thrombogenic effects of atorvastatin in acute ischemic stroke. Neural Regen Res. 2013;8(23):2144-54. doi: 10.3969/j.issn.1673-5374.2013.23.004.
108. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation. 1999;100(3):230-5. doi: 10.1161/01.cir.100.3.230.
109. Bełtowski J, Wójcicka G, Jamroz-Wiśniewska A. Adverse effects of statins-mechanisms and consequences. Curr Drug Saf. 2009;4(3):209-28. doi: 10.2174/157488609789006949.
110. Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. Diabetologia. 2006;49(8):1881-92. doi: 10.1007/s00125-006-0269-5.