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Dyslipidemias and Role Of Statins In Their Therapy.

Dalal Daham AL-Otaibi, and Ladislav Novotny*.

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University, Kuwait.

ABSTRACT

Dyslipidemias or abnormal lipid levels in the blood represent a major risk factor for cardiovascular disease (CVD) development. Dyslipidemias are classified based on their nature as primary or secondary. Prolonged dyslipidemia may result in atherosclerosis, a multifactorial process that leads to a reduction of blood flow and contributes to CVD. Dyslipidemias contribution to atherosclerosis is based on an enhancement of so called pro-atherogenic state. Fortunately, effective drugs, statins, also called HMG reductase inhibitors, can be used to treat dyslipidemias. Statins inhibit the rate limiting step in cholesterol biosynthesis as they block hydroxylmethylglutaryl coenzyme A (HMG-CoA) reductase. Additionally, statins have pleiotropic effects that play a role in CVD prevention not related to cholesterol level. Statins were shown to benefit patients with Alzheimer disease, cataract, pulmonary diseases and they also possess antiviral activity. Chronic liver disease is not a contraindication for use of statins, whereas acute liver failure is.

Keywords: dyslipidemia, cardiovascular disease, statins

Corresponding author

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INTRODUCTION

An abnormal concentrations of the lipids in the blood represent dyslipidemia. As such, it is the most prevalent and manageable risk factor for atherosclerosis. Proper treatment of dyslipidemia can reduce the risk of many CVD diseases (peripheral arterial disease, revascularization procedures, nonfatal myocardial infarction, stroke, and cardiac death) [1]. The National Health Nutrition Examination Survey (NHANES) demonstrated an increase in dyslipidemia incidence with increasing body mass index. It was shown the 19% of obese people are likely to have dyslipidemia [2]. There is no specific symptoms of dyslipidemia. However, the patients may complain of xanthomas, paresthesias, confusion and dyspnea [3]. In general, there is poor awareness of problems and conditions related to dyslipidemia among some groups of population [4]. Dyslipidemia is diagnosed by measuring the total plasma cholesterol levels, triglycerides and the individual lipoproteins in the blood. The fasting lipid concentrations (mg/dl) that are deemed healthy are <200 mg/dl of total cholesterol, <150 mg/dl of triglycerides, < 100 mg/dl for low density lipoproteins (LDL) and > 40 mg/dl for men and >50 mg/dl women of high density lipoproteins (HDL) [5]. The presence of CVD and risk factors for CVD lead to changes in these concentrations [5]. The risk factor of CVD that are non-modifiable include age, gender and family history. Modifiable CVD risk factors include hypertension, diabetes, dyslipidemia, obesity and diet [5,6].

Treatment of dyslipidemia consists of two significant lifestyle modifications – diet and exercise, in an addition to drug therapy. In general, the type of dyslipidemia treatment depends on the age, symptoms, adherence, and cardiovascular risk evaluation [3,5,6]. Due to the complementary effects of diet and exercise on the lipid profile, they are recommended for patients with mild dyslipidemia [3,6]. Diet, in which caloric intake from fat is less than 30% (and less than 8% - 10% from saturated fat) of the total calories, contribute to a more significant decreased of total cholesterol and LDL (approximately 7% each). Introducing exercise into lifestyle may contribute to an increase in HDL by more than 2% and a decrease in TG by 12% [6,7]. However, this type of diet (with less than 20% energy from fat) adversely affects the lipid profile of the patient [6,7].

Pharmacotherapy with statins, cholesterol absorption inhibitors, bile acid and nicotinic acid helps with achieving therapeutic goals [7]. Statins as powerful LDL-lowering drugs are widely used. They inhibit 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase with the consequent effect of up to 60% LDL reduction [6]. After an introduction of lovastatin, several other statins were developed and introduced to patients. It is now acknowledged that ability of statins to reduce cholesterol concentration differs among different statins types. The most potent statin is cerivastatin followed by rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin and fluvastatin [8]. Dose of the statins should be individualized according to the patient characteristics and goals of the therapy, response and patient's liver and renal function [6,8]. At present, statins are the effective agents used for reduction of the incidence of cardiovascular mortality and morbidity in high risk patients [8].

FATE OF LIPIDS IN ORGANISM AND DYSLIPIDEMIAS

Lipids are necessary for maintaining integrity of cellular membranes and for biosynthesis of bile acid and steroids. Being water-insoluble, lipids circulate in the blood in association with a large carrier protein forming spherical water soluble lipoprotein particles that vary in size and density. According to the size lipidic particles of the blood are classified divided into 4 basic groups: chylomicrons containing 97-99% of lipids, very low density lipoproteins – VLDLs -containing 90-95% of lipids, low density lipoprotein – LDLs – containing 75-80% of lipids and high density lipoproteins – HDL – containing 55% of lipids [9]. Various lipoproteins possess on their surface different types of surface proteins that are called apolipoprotein (Apos). Apos have different functions, such as secretory, they serve as ligands to bind to receptors on the cell surface or they function as cofactors necessary for enzymes taking part in the removal of triglycerides (TGs) from chylomicrons and VLDL [9]. In general, two pathways are distinguished in lipid metabolism: endogenous and exogenous. If the lipoprotein particles are composed mainly of dietary (exogenous), the metabolic pathway is classified as exogenous. The metabolic pathway is classified as endogenous when lipids in question originate in the liver through de novo synthesis of triacylglycerols.

In exogenous pathway, dietary lipids are emulsified by bile into micelles. Then TGs are degraded by pancreatic lipase to two fatty acid molecules and one 2-monoacylglycerol. The molecules created are absorbed by enterocytes and transformed again into TGs and chylomicrons with AposB-48, AposC, and AposE are assembled. These nascent chylomicrons are moved by secretion to lymphatic system. Chylomicrons bypass the liver when circulating in lymph, from which they enter into the blood. Nascent chylomicrons then obtain ApoC-

II and ApoE from HDLs and as such are considered mature. They then activate lipoprotein lipase (LPL) and TGs are again hydrolyzed. The products of TGs hydrolysis (glycerol and fatty acids) undergo absorption in peripheral tissues and they serve as a source of energy. Mature chylomicrons that lost TGs are called chylomicron remnants. They are hydrolyzed within lysosomes and glycerol and fatty acids within body cells are also used as an energy source or the form of energy stores [1,9,10].

The liver also produces specific particles in the endogenous pathway as it is able to store glycerol and fats in hepatocytes. Hepatocytes are able to synthetize TGs via *de novo synthesis* and they produce the bile from cholesterol. Hepatocytes assemble nascent VLDLs particles from TGs, cholesterol and cholesteryl. Nascent VLDLs are equipped with ApoB-100 that help their release into the blood. In the blood, nascent VLDLs mature through their interaction with HDLs, from which their obtain Apo C-II and ApoE. LPL of endothelial cells is activated by ApoC-II and VLDLs are hydrolyzed similarly to the exogenous pathway. VLDLs remnants with a relatively high cholesterol content (60-70%) are absorbed by the liver and peripheral cells through endocytosis [5,6]. About 80% of the circulating LDLs re-enters the liver through the B-100 receptor and the remaining 20% remain in peripheral tissue. Some of these 20% are taken up by macrophages and contribute to atherosclerosis [1,9,10].

A very important process takes part in the body and it is called reverse cholesterol transport. This process enables cholesterol to be transported from the arterial walls and the other extra-hepatic tissues back to the liver by HDL particles [11]. The process involves some lipoproteins and is beneficial for the body as it helps to fight dyslipidemia.

Dyslipidemias are of primary or secondary origin [1,4]. Primary dyslipidemias are caused by overproduction of the cholesterol; defective cholesterol, LDL or triglyceride clearance; and by underproduction or excessive clearance of HDL or defective cholesteryl ester transfer protein (CETP). Secondary dyslipidemias may be reflecting process related to other diseases, such as diabetes mellitus, chronic kidney disease, primary biliary cirrhosis, or they may be a result of pharmacotherapy with beta blockers, thiazides and retinoids [1,4]. In general, these dyslipidemia result in increased cholesterol, TGs, LDLs and/or VLDLs and in a decrease of HDLs.

DEVELOPMENT OF ATHEROSCLEROSIS

Atherosclerosis is a severe consequence of abnormal cholesterol levels. At atherosclerosis, cholesterol forms plaques within arteries. This process leads to obliteration of blood flow to tissues [12-14]. Atherosclerosis is a multifactorial disease based on a complex process that is responsible for almost one fourth of deaths in the USA [15]. The incidence is increasing in women due to smoking, dietary habits and diabetes [16,17] but it is more common in men. Inflammation is the most important factor. Other risk factors for atherosclerosis are diabetic, hypertension, age, family history of heart attack, and abnormal elevated of cholesterol [12,13].

Atherosclerosis develop after migration of the LDL from endothelial cells to the arterial intima. However, even if the amount, or concentration, of LDL in the arterial intima is about 10 times higher than in any other connective tissue in the body, the intima will look and act normally. The first step in the atherosclerosis development starts when the LDL particles change and form deposits of cholesterol and other lipids [18]. The retained LDL is the cause of atherosclerosis. Arterial intima has more retained LDL due to lack of the lymph system. However, new research reports that collagen, elastin, and proteoglycans play a role in attracting and retaining the LDL [19]. Retained LDL in the intima are suspect-able for chemical alteration that leads to structural modification of the LDL by enzyme or reactive oxygen species [19]. This oxidize LDL will lead to disturbed production of nitric oxide (NO, vasodilator,) through an increase in caveolin-1. This negatively affects endothelial nitric oxide synthase (eNOs) activity [20]. Additionally, the cell adhesion molecules on the vascular endothelial cells, such as vascular cell adhesion molecule-1 (VCAM-1), are selectively expressed and vascular smooth muscle apoptosis is promoted. To deal with the damage, smooth muscle cells migrate and proliferate within the damage area and activate T-lymphocytes. Lymphocytes and monocytes than penetrate the intima. The lymphocyte-activated monocytes consequently differentiate into macrophages enhancing the uptake of oxidized LDL by a scavenger receptor - CD36 [12,18,19]. After the accumulation of oxidized LDL in the macrophages, the foam cell will develop and form fatty streak. The fatty streak, which is a flat yellowish streak or has a form of dots, does not cause damage. However, it is the first stage in the atherosclerosis development.

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Foam cell will secrete cytokines, IL-6 (interlukin-6), IFN-Y (interferon γ) and interferon alpha (TNF-α), and also inflammatory mediators. All of these results in additional impairment of endothelial functions [12,18,19].

The second step of the atherosclerosis development is the accumulation of the foam cells. This leads to formation lipid-rich core ''transition lesions''. The third step is the fibrous plaque formation [8,12,18,19]. Unlike fatty streak, fibrous plaque has thickened lesion and cholesterol-rich core. The core region contains many dead cells and is covered by a fibrous cap. Consequently, additional cholesterol (and other lipids) deposition may occur in the healthy tissue between the core and endothelia cells leading to a plaque rupture [18,19].

It is know now that dyslipidemia promotes atherosclerosis through enhancing pro-atherogenic state by increasing LDLs, small dense LDLs, IDLs, oxidize LDLs and chylomicron remnants. However, high HDL level has a protective and anti-atherogenic as well anti-inflammatory and anti-oxidant effects [9,11]. However, it is necessary to stress that high HDL levels were detected in some patients suffering from various complications of cardiovascular diseases [11].

STATINS AS CHEMICAL AND PHARMACOLOGICAL SUBSTANCES

The statins structure is closely related to HMG-CoA reductase as they are a group of competitive antagonists of this enzyme. Statins produce an inhibition of cholesterol synthesis through their interference with mevalonate pathway. Their pharmacological action results in a decrease of LDLs, TGs and total cholesterol in serum as well as in an increase of HDLs [21-23].

The essential part of any statin molecule is a dihydroxyheptanoic acid unit and a ring system with various substituents. A hydroxyglutaric acid component of statins structure represents the pharmacophore for these drugs (Fig.1). The similarity to endogenous substrate HMG CoA is obvious. The statin pharmacophore binds to the same active site as the substrate HMG-CoA and inhibits the HMG-reductase enzyme. It has also been shown that the HMG-reductase is stereoselective. Consequently, 3R,5R configuration is necessary for biological activity of all statins used for their cholesterol-decreasing activity [24].

Statins differ in their substituted ring structure. The parameters that are being attempted to be improved in new drugs are affinity for the active site of the target enzyme, relative distribution of a substance in the liver and non-hepatic tissue, parameters of systemic circulation and availability for non-hepatic tissue and parameters of metabolic degradation and elimination.

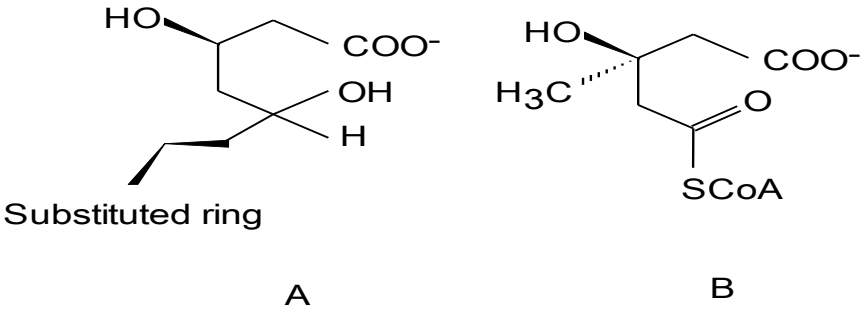

Figure 1: Similarity of structure of statins' pharmacophore (A) and HMG-CoA (B)

Traditionally, statins are divided into two main groups according to their ring structure and its substitution:

1. Type 1 statins (lovastatin, pravastatin, simvastin and sometimes also mevastatin): These compounds contain a substituted decalin ring. The butyryl group is an essential component of type 1 statin structures [25].

2. Type 2 statins: These are totally synthetic substances, usually with a relatively large substituents linked to HMG-like moiety. In these molecules, the butyryl group is replaced by the fluorophenyl group responsible

for additional polar interactions resulting in stronger binding to the HMG-reductase [25,27]. Fluvastatin, cerivastatin, atorvastatin and rosuvastatin belong among type 2 statins.

Statins inhibit HMG-CoA reductase in a competitive, dose-dependent, and reversible manner. Their structure is based on a hydrophobic ring system that is responsible for the binding to the HMG-CoA reductase in a manner that prevents binding of the natural substrate [26,27]. There is a relative variety of rings in the structure of the type 2 statins as it may be an indol ring (fluvastatin), a pyrrol ring (atorvastatin) or a pyrimidine ring (rosuvastatin) [27]. At the moment, rosuvastatin is considered to be the most efficient statin as it, due to its structure, enters into additional hydrogen binding interactions that increase the binding to the HMG-CoA reductase [26,27].

PHYSICO-CHEMICAL PROPERTIES OF STATINS

Physical properties of statins determine the extend of drug absorption, onset of action, metabolism and bioavailability etc. (Table 1). Statins are absorbed rapidly and reach the peak plasma concentration within 4 hours. However, the daily absorption changes in the relation to the time of administration and food intake [26]. Statins with short half-lives are taken at night because the activity of HMG-CoA reductase and cholesterol biosynthesis occur at night, whereas statins with long half-lives cane be taken any time [35,36]. Since the liver is the target organ, most of the statins have the first pass effect uptake. This affects the systemic bioavailability of statins and their metabolites. As a result, systemic bioavailability of statins and their metabolites varies from 5 to 30% [26,37].

Lipophilicity is a very important characteristic in determining therapeutic effect statins. Lipophilic statins are suspected to cause muscle pain notably more than hydrophilic statins [26]. An increase in lipophilicity leads to increased concentrations of a statin in both hepatic and non-hepatic tissues and it also enables them to cross the blood-brain barrier. On the other hand, statins with lower lipophilicity/higher hydrophilicity tend to be more hepatoselective. This is because statins with higher hydrophilicity transported in a higher extent into hepatic tissue by active transport of organic anion transporting polypeptide (OATP). More lipophilic statins diffuse passively and non-selectively into both hepatic and non-hepatic tissues. Most hydrophilic statins are pravastatin and rosuvastatin due to the presence of polar hydroxyl groups and methane sulphonamide group respectively [26,31, 38].

PHARMACOLOGICAL ACTIONS OFSTATINS – CHOLESTEROL-LOWERING EFFECTS

The main therapeutic effect of statin is based on inhibition of the processes that constitute endogenous mevalonate pathway and that represent the first committed step in the biosynthesis of cholesterol. The key and rate-limiting step in cholesterol biosynthesis is the conversion of HMG-CoA to mevalonate mediated by HMG-CoA reductase [26]. The inhibition of HMG-CoA reductase by statins impairs the production of cholesterol. As the most of the circulating cholesterol comes from the liver rather than the diet, statins act by inhibiting cholesterol synthesis from the liver. The reduced cholesterol level in the liver consequently activate the cellular signaling cascade culminating in the activation of sterol regulatory element binding protein (SREBP), which is a factor responsible for up-regulating expression of the gene encoding the LDL receptor. As a result, the liver cells attempt to compensate for the reduction in the cholesterol level by synthesizing more LDL receptors on the cell surface to increase cholesterol uptake from the blood. Then, LDL and VLDL particles bind to and enter the liver cells, where the cholesterol component is processed into bile salts. After that, LDL and VLDL will be excreted or recycled [34]. Moreover, synthesis of isoprenoids is also impaired as a result of inhibition of the HMG-CoA reductase. This leads to the impairment of several process, namely selenocysteine tRNA isopentenylation (this may be the cause of muscle pain), dolichol-mediated *N*-linked glycosylation, isoprenylation of small GTPase proteins (Ras, Rho, Rab and Rap) by decreasing farnesyl-pyrophosphate (FPP) and geranylgeranyl-pyrophosphate (GGPP) (important lipid attachment molecules) and coenzyme Q10 tail synthesis [27,39,40].

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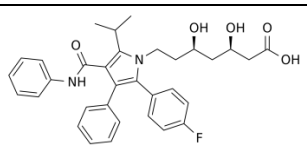
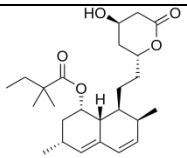
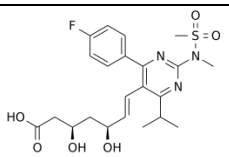
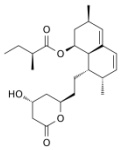
Table 1: Physico-chemical properties for commonly prescribed statins.

	Atorvastatin	Simvastatin	Rosuvastatin	Lovastatin
Structure				
Chemical formula	$C_{33}H_{34}FN_2O_5$	$C_{25}H_{38}O_5$	$C_{22}H_{28}FN_3O_6S$	$C_{24}H_{36}O_5$
Molecular weight	557.6	418.6	481.5	404.5
Solubility	Lipophilic	Lipophilic	Hydrophilic	Lipophilic
Bioavailability	12%	5%	20%	5%
Food effect	↓Bioavailability	No effect	No effect	↑Bioavailability
Protein binding	>98% bound to plasma proteins	Both simvastatin and its β-hydroxyacid metabolite are highly bound (approx. 95%) to human plasma proteins.	88% bound to plasma proteins. Binding is reversible and independent of plasma concentrations.	Lovastatin and its β-hydroxyacid metabolites are highly protein bound (>95%).
Active metabolite	2-hydroxy- and 4-hydroxy-atorvastatin acid	*β*-hydroxyacid and its 6′-hydroxy, 6′-hydroxymethyl and 6′-exomethylene	---	---
CYP 450 metabolism	3A4	3A4	Not metabolized by CYP 450	3A4
Route of elimination	Eliminated primarily in bile after hepatic and/or extrahepatic metabolism. Does not appear to undergo significant enterohepatic recirculation. Less than 2% of the orally administered dose is recovered in urine.	13% of the dose was excreted in urine and 60% in feces.	Orally rosuvastatin and its metabolites are primarily excreted in the feces (90%)., I.V dose approximately 28% of total body clearance via the kidney, and 72% by the hepatic route.	It undergoes extensive first-pass extraction in the liver. 83% of the orally administered dose is excreted in bile and 10% is excreted in urine.
Half-life (h)	14	2	19	3
Dosage form	Tablets 10, 20, 40, 80 mg	Tablets 5, 10, 20, 40, 80 mg	Tablets 5, 10, 20, 40 mg	Tablets 10,20,40 mg

CYP 450 - cytochrome P450;
From references [26,28-34].

PHARMACOLOGICAL ACTIONS OFSTATINS – PLEIOTROPIC EFFECTS OF STATINS

Pleiotropic effects of a drug can be defined as the actions related or unrelated to the primary mechanism of the drug therapeutic action. Pleiotropic effects can be undesirable or neutral or beneficial. Beneficial pleiotropic effects of statins are independent of their cholesterol lowering effect but some of them are related to the HMG-CoA reductase inhibition and occur at low concentrations [41]. Pleiotropic effects of statins have a role in cardiovascular disease prevention. Cholesterol-independent effects of statins are due to the ability of statins to release anti-atherogenic cytokines such as IL4 and IL10 [42].

IMPROVEMENT OF ENDOTHELIAL DYSFUNCTION

Increased NO bioavailability

Endothelial dysfunction is one of the consequences of the atherogenic process that is characterized by decreased NO activity. Endothelial dysfunction occurs due to imbalance between vasodilating substances (NO and prostacyclin) and vasoconstricting substances (endothelin-1 and angiotensin-II) [41]. Statins inhibit transcription of endothelin-1, which is elevated in advanced atherosclerosis and endothelial dysfunction. Moreover, Statins affect endothelial function positively by inhibiting down-regulation of the eNO, responsible

for producing NO from L- arginine [41,43]. Moreover, statins increase the bioavailability of NO by several mechanisms [41]:

1. Reduction of the caveolin-1 that is an inhibitor of eNO activity.
2. Facilitating the long term activity of the eNO by increasing heat shock protein-90 (Hsp 90) which is a singling mediator of NO [43].
3. Decreased production of reactive oxygen species which inactivate NO.
4. Prolonging of eNO-mRNA half-life by inhibition of small GTPase proteins.
5. Activation of serine/threonine kinase Akt that is responsible for phosphorylation of the eNOS leading to increased NOS activity.

Antioxidant effects of statins

Hydroxyl metabolites of atorvastatin inhibit the oxidation of LDLs, VLDLs and HDLs. Statins are also able to decrease the activity of macrophage CD36 that indirectly leads to decrease in lipoprotein oxidation, but the mechanism of this is still under investigation [41].

ANTIINFLAMMATORY EFFECTS OF STATINS

It is no generally accepted that inflammation represents a major risk factor for developing atherosclerosis. Inflammation is based on interaction between blood leukocytes and vascular endothelium. An increase in cholesterol concentrations leads to expression of cell adhesion molecules. The occurrence of inflammation can be detected using biochemical markers that are elevated in this situation. These biochemical markers are C-reactive protein (CRP), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis-alpha (TNF-α). The anti-inflammatory effect of statins is characterized by decreasing CRP early and independently of the cholesterol lowering effect [40]. In a study on 22 patients with combined hyperlipidemia, it was found that pravastatin, simvastatin and atorvastatin significantly decreased high sensitive CRP. In another study simvastatin was found to have early beneficial effects in acute coronary syndrome by decreasing CRP within 14 days [41].

Another biochemical marker for inflammation that can also be reduced by statins is cell adhesion. Many studies have examined the effect of statins on adhesion molecules. However, the obtained results are inconsistent [41].

PLAQUE STABILIZATION

Plaque composition and stability have a role in determining possible consequences of atherosclerosis. Statins facilitate decrease of cholesterol accumulation either by decreasing availability of free cholesterol or by reducing cholesterol synthesis [44]. Statins can cause the stabilization of plaques by several mechanism. Statin use may result in reduction of lipids and oxidizing LDLs, in reducing numbers of macrophages, T cells and MMP2 (matrix metalloproteinase-2 or type IV collagenase or gelatinase A) immunoreactivity and apoptosis of vascular smooth muscle cells (lipophilic statins only) by inhibiting protein prenylation. Inhibition of MMP2 leads to increase in collagen content [41].

ANTI-PLATELET ACTIVITY

An increase in cholesterol levels enhances platelet aggregation due to increased adenosine-diphosphate that can induce fibrinogen binding to platelets. Statins inhibit platelet aggregation by decreasing LDL levels or by changing cholesterol content in the platelet membrane. Atorvastatin decreases platelet activation without affecting cholesterol level [44].

BONE MINERAL DENSITY

The use of statins leads to an increase in deposition of minerals in bones through inducing expression of bone morphogenetic protein 2 (BMP-2, belongs to the TGF-β superfamily of proteins). This protein has bone forming activity [44]. Moreover, statins inhibit resorption of minerals by reducing prenylation of GTP-binding proteins .This blocks activity of osteoclasts and inhibits their apoptosis [45].

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OTHER EFFECTS OF STATINS

Various studies have shown that statins produce effects similar to that of vascular endothelial growth factor, which plays a role in neovascularization and in augmenting endothelial progenitor cell (EPC) differentiation. EPCs are one of the key elements essential for recovery from ischemic injury. Statins facilitate circulation and mobilization of EPCs to the injury site. Atorvastatin (daily dose of 40mg) is able to increase the number of EPCs after one week of treatment in patient with stable coronary artery disease [41].

Statins may also act as immunomodulators. In cardiac transplant patients, pravastatin combined with an immunosuppressive drug can increase survival and decrease the rejection frequency [41].

Statins have a protective effect on organs such as kidney and pancreas. Administration of simvastatin (2mg/kg/d for 4 weeks) reduces cardiac hypertrophy induced by angiotensin II infusions and trans-aortic constrictions [41].

Antiviral and antibacterial effects of statins have also been reported. A Canadian study found that statins are able to suppressed the attachment of HIV to potential host cells [46].

The evaluation of the rate of sepsis among patients hospitalized for heart incidents found that a the rate of sepsis in statin users had 19% lower than that of the non-statin users during the two-years period following the hospitalization [46]. Incidence of pneumonia and cataract was also found to be decreased among statin user compared to non-statin users [46]. I was also reported that as statins lead to an increase in HDLs, patients with dementia and Alzheimer's disease may also benefit from their administration [11].

EVALUATIONS AND TESTS PERFORMED BEFORE PRESCRIBING STATINS

Statins may cause undesirable or even harmful side effects. Consequently, the health care provider take measures to reduce statins' intolerance. The aim of performed evaluation is to identify patient that are at high risk of developing some adverse effect related to stain's use. These measures include comprehensive pretreatment assessment, ongoing monitoring and patient counseling. Pretreatment assessment includes personal and family history, physical examination, and lab investigation. Several risk factors should be considered before prescribing statins to avoid statin-associated side effects. These risk factors are classified into endogenous and exogenous as shown in Table 2.

Table 2: Risk factors for developing statin-related side effects.

Endogenous risk factor	Exogenous risk factor
Advanced age (more than 80)	High statin dose
Female sex	Alcohol abuse
Asian ethnicity	Illicit drug use (cocaine, amphetamines)
Low body mass index	Antipsychotics
History of pre-existing/unexplained muscle/joint/tendon pain	Fibrates (particularly gemfibrozil)
History of creatine kinase (CK) elevation	Nicotinic acid
Family history of myopathy	Amiodarone, Verapamil, Warfarin,
Family history of myopathy with statin therapy	Heavy and/or unaccustomed exercise
Metabolic muscle disease	Nefazodone
Severe renal disease	Surgery with severe metabolic demands
Acute/decompensated hepatic disease	Large quantities of grapefruit
Hypothyroidism (untreated)	Protease inhibitors
Diabetes mellitus	Azole antifungals
Genetic polymorphisms of CYP enzymes	Macrolide antibiotics

Adapted from [40].

There are some genetic factors that may contribute to an enhancement of statins-related side effect. DNA polymorphism in the genes encoding CYP 450 enzyme, intestinal P-glycoprotein, and OATP increases the susceptibility to statins' intolerance. Genetic tests are not approved to prevent or manage these statins-related side effects [40].

Liver function test (LFT) and creatine kinase (CK) levels should be established before starting statin therapy in a patient [40]. It is important to stress that statins are not contraindicated in patients with chronic liver disease [47]. As nonalcoholic fatty liver (NAFLD) is the most common liver disease in American and European populations, it is well established that percentage of NAFLD increases due to obesity, overlap metabolic syndrome and diabetes in population [47]. NAFLD may lead to hepatic steatosis, portal inflammation, sinusoidal fibrosis and ballooning hepatocytes containing Mallory's hyaline [47]. Ballooning hepatocytes and fibrosis may progress to cirrhosis. Also, NAFLD increases risk of cardiovascular disease, especially in patient with diabetes.

As a result, the patients with NAFLD benefit significantly more from statin therapy compared to possible risks [47]. Even in cirrhosis development, statins are able to decrease morbidity and mortality by decreasing portal hypertension [47ok]. Moreover, statins are considered to be beneficial in chemoprevention of hepatocellular carcinoma that represents a complication of cirrhosis. However statins are contraindicated in patients with acute liver failure [47].

As some statins are excreted via renal pathway, baseline creatine and GFR need to evaluated. Moreover, secondary causes of dyslipidemia should be excluded before starting statins therapy [40].

STATINS AS PROPHYLACTIC AGENTS

CVD is a heart and vessels disease and the leading cause of death [48]. Many studies indicate that incidence of CVD increases with elevated level of lipids [48]. Several studies were published dealing with benefits of statin prescription. Currently, patient who have 20% or greater 10-years risk of developing CVD are recommended to take simvastatin 40 mg as primary prevention [49]. A study indicates that statins decrease the relative risk of occurrence of coronary events, cardiovascular disease mortality, non-fatal strokes and all-cause mortality [49]. It is also being recommended for atorvastatin 20 mg to be used as primary prevention for patients at 10% risk of CVD [50]. This study found that statins reduce CVD in patients who do not have evidence of CVD [50]. Patients who have evidence of CVD or diabetes aged over 40 should take Simvastatin 40 mg [49]. In general, the use of statins in CVD therapy is associated with improvement of CVD mortality and morbidity [48]. As for today, NICE guidelines recommends atorvastatin 80 mg as secondary prevention of CVD [49,50]. It was shown that statin therapy does not affect incidence of cancer in patients [51].

ADVERSE EFFECTS OF STATINS

Although statins are generally safe and well tolerated, they may exhibit some side effects. Muscle complaints are the major and the most commonly reported adverse effects and are the main reason for discontinuing statin therapy. Muscle complaints start from myalgias and end with rhabdomyolysis [40]. Myopathic reaction can be induced by toxic metabolism or, in rare situations, by immune response. Toxicity is due to the disruptive effect of statins on small G-protein function by reducing isoprenoid intermediaries. Consequently, protein handling and gene expression are altered. The severity of the muscle breakdown can be determined using hyperCKemia classification [40]. This classification divides the statin-related muscle side effects into grad 1 and grad 2 groups.

Grade 1 patients have concentrations of creatine kinase (CK) between normal and less than 5 times of upper limit of normal (ULN) values. These patients may or may not suffer from myositis.

Grad 2 patients are divided into 3 subsets based on CK levels. Grade 2a is classified as mild and CK concentrations are between 5 and 10 times of ULN. These patient may or may not have myositis but the statin therapy has to stopped. Grade 2b is classified as moderate and CK concentrations are between 10 and 50 times of ULN. These patient may or may not have rhabdomyolysis with/without renal dysfunction. Grade 2b is classified as severe and CK concentrations are higher than 50 times of ULN. These patient may or may not have rhabdomyolysis with/without renal dysfunction [40].

Myalgia is associated with flu-like symptoms which may develop within 6 months after starting statins. Myalgia usually exists in the proximal musculature and resolves within 2 months of discontinuing the statins. Rhabdomyolysis is the most severe adverse effect associated with muscle pain, dark urine and

tenderness on palpation [40]. Additionally, acute renal failure, hyperkalemia, hypocalcemia and cardiac arrhythmia or arrest are the consequences of the rhabdomyolysis. The risk of developing rhabdomyolysis is 0.3 per 100 000. However, this risk increases, if the statins are combined with fibrate therapy for dyslipidemia [39]. Moreover, the rhabdomyolisis risk is increased by concomitant use of cytocrom-P450 (CYP450) inhibitors (verapamil, diltiazem, azoles antifungals, macrolides, and grapefruit) that decrease statins metabolism. On the other hand, pravastatin and rosuvastatin are unaffected by these drugs, as they are not metabolized by CYP450 [40].

In addition, statins may cause transient, asymptomatic, dose-related and spontaneous resolving adverse effects such as elevated liver enzymes values AST and ALT to greater than 3 times of the ULN [40]. The common hepatic adverse effects have been reported is transaminitis defined as increased transaminases (AST, ALT) coupled with non-specific hepatitis, which may occur in a patient undergoing the early stages of multiorgan failure. The elevation of transaminases is not accompanied by histopathological changes [39]. This adverse effect is generally rare and unrelated to the reduction of LDLs [40].

However, statins will not normally cause liver failure so routine liver function test is not recommended, but it should be performed 6-12 weeks after initiation of therapy and upon any increased dosage. If the liver enzymes are increased more than 3 times of ULN, statin therapy is discontinued.

Many studies report that statins may worsen insulin sensitivity in non-diabetic patients. A small increased risk of developing type2 diabetes was associated with statin therapy [40]. Moreover, statins have potential neurological effects leading to decline of memory function. FDA does not recommend discontinuing statins even if the patient complains from memory dysfunction because these effects are reversible and the benefit from statins for the heart are greater than the risks [40,52]. Additionally, statins cause deficiency in coenzyme Q10 by inhibiting HMG-CoA that is responsible for producing coenzyme Q10 precursor and will therefore lead to the decrease in energy production. As a result, impairment of myocardial function, liver dysfunction and myopathies are seen in patients on statin therapy. Consequently, it is recommended that statin therapy is combined with supplementation of coenzyme Ql0 [39].

Occasionally, some other side effects are being reported. The recommendation for the treating physician is that if the patient cannot tolerate side effects of the statin therapy, changing the dose time, decrease of the dose and change of the statins type is recommended [26,40].

PRESCRIBING OF STATINS

In many countries, i.e. United Kingdom, statins have become one of the most commonly prescribed OTC drugs [53]. Their use as a prophylactic agent is also actively encouraged [53]. The American College of Cardiology and the American Heart Association have published new guidelines for the use of statins that recommended statin as a prevention therapy in patient with CVD, LDLs concentration of more than 190 mg/dl, type 2diabetes and age between 40 and 75 years [54].

CONCLUSIONS

In conclusion, dyslipidemia is a disease characterized by elevation of the cholesterol and lipoproteins concentrations in the blood. Dyslipidemia may lead to atherosclerosis - a risk factor for CVD. Statins, HMG-CoA reductase inhibitors, are a class of drug that can be used to treat dyslipidemia. Simvastatin and lovastatin are examples of pro-drug statins that are converted to beta hydroxyl acid by liver. Lipophilicity is one of the statins properties affecting selectivity. Hepatoselectivity of statins increases in hydrophilic statins, while lipophilic statins also tend to enter non-hepatocyte cells through passive diffusion. Rosuvastatin and pravastatin are two examples of hydrophilic drug.

Differences in chemical structure of statins cause variation in the affinity to the active site, entrance rate into hepatic and non-hepatic cells and also their transformation and elimination. At present, statins have an expanded role in therapy, beyond the original inhibition of cholesterol synthesis. Statins are used in primary and secondary prevention of CVDs, for an improvement of endothelial functions, as antioxidant and anti-inflammatory agents, as immunomodulators, for their plaque stabilization properties and anti-platelet activity and as inducers of BMP2 expression and inhibitors of osteoclast and osteoblast apoptosis. Consequently, these

cholesterol-lowering drugs benefit much broader spectrum of patients than originally intended. However, dyslipidemias and high cholesterol remain the main conditions for their use in general population.

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