Statins and Cholesterol: A Perspective Revisited

Authors
Dr Varshiesh Raina¹, Dr Konika Razdan²

¹Lecturer, Sanjeevni College of Nursing and Paramedical Sciences, Jammu, J & K
²VRDL, Department of Microbiology, Govt. Jammu Medical College, J & K

Corresponding Author
Dr Varshiesh Raina

Over the past 36 years, the global market has witnessed a substantial demand for Statins. As a result Statins have proved to be a highly profitable and lucrative market in pharmaceutical sector. This rise in statin consumption has been mainly recognized due to its cholesterol lowering effect, particularly, the low density lipoprotein (LDL) cholesterol in the body.¹ Increased levels of LDL are considered to be one of the major risk factor that predisposes heart patients towards heart attack. Noticeably, heart disease is the number one cause of death in U.S and, increasing, worldwide. A large number of placebo-controlled studies showed that Statins can substantially reduce mortality in high risk patients, but no history of heart disease. The American Heart Association and the American College of Cardiology have provided guidelines wherein Statin treatment should be used for primary prevention of cardiovascular disease in adults with a 10-year risk of developing heart attack or stroke of 7.5% or more; LDL cholesterol ≥ 190 mg/dL or those with diabetes, age 40–75 with LDL-C 70–190 mg/dL.² The safety of statins became noticeable when cerivastatin was withdrawn worldwide in August 2001 as it caused fatal rhabdomyolysis.³ In this review article we will be emphasizing on the studies which will underpin the risks associated with statins from cholesterol point of view.

Discovery of Statins

As the evidence grew that the hypercholesterolemia is major risk factor for coronary atherosclerosis, scientists across the world began to unlock the pathway that was involved in the biosynthesis of cholesterol. It was around 1950s, when four biochemists—Konrad E. Bloch, Feodor Lynen, John Cornforth and George Popjak unveiled 30 enzymatic reactions critical for cholesterol biosynthesis.⁴ The cholesterol biosynthesis involves four stages and the third reaction in first stage (i.e., reduction of HMG-CoA to mevalonate) governs the rate limiting step.

Around 1960s, the cholesterol pathway was completed elucidated and at the Nobel Banquet in Stockholm, December 10, 1964, the Bloch and Lynen were honored with the Nobel Prize. This was the time when researchers in both academia
and industry began venturing into molecules that could target any step in cholesterol biosynthetic pathway. In 1959, Triparanol (which inhibited the final stage in the cholesterol synthetic pathway) was the first such candidate molecule that entered into the clinical trials in the U.S market; however it was withdrawn in 1960 because of the numerous side effects like cataracts and accumulation of other sterols.\(^5\)

Around 1955, a Canadian pathologist Rudolf Altschul discovered cholesterol lowering effect of nicotinic acid.\(^6\)

At Imperial Chemical Industries (ICI) laboratories in England, researchers synthesized Clofibrate and many derivatives of clofibrate, called fibrates, that showed cholesterol lowering properties and were safe to use.\(^7\)

Unfortunately, the modes of action of these synthetic derivatives were not well understood. Cholestyramine (a bile acid sequestrant) was introduced, which lowered plasma cholesterol by converting it to bile acids.\(^8\)

However, the Cholestyramine was not well tolerated by all patients. One of the major drawbacks of these molecules reported so far was that none of them was effective in terms of safety or efficacy. This refined the search to look for molecules that could specifically block early steps of cholesterol biosynthetic pathway and display better therapeutic properties.

In 1971, at Sankyo Research Laboratories, Tokyo, Japan, a scientist named Akira isolated the first HMGCoA reductase inhibitor i.e., Citrinin, from active culture broth of 3800 strains of fungi.\(^9\)

The Citrinin showed cholesterol lowering properties in experimental rat models but unfortunately, it was toxic to the kidneys. The discovery of Citrinin opened a ray of hope to look for other molecules in culture broths of molds that might display cholesterol lowering properties. Fortunately, Compactin in (ML-236B) was isolated from active broth of *Penicillium citrinum* which was an extremely potent inhibitor of HMG-CoA reductase.\(^10\)

Further studies revealed that the structure of Campactin was similar to HMG-CoA and acted as a competitive inhibitor for HMG-CoA reductase.

**Structure similarities between HMG-CoA and Compactin**

In order to substantiate, the efficacy of Compactin, Akira along with his colleagues performed some in-vitro and in-vivo experiments.\(^11\)

Their in-vitro experiments with mammalian cells showed that at high concentration of Compactin, the cells were unable to grow and died which was overcome by adding a small amount of mevalonate (the product of the HMG-CoA reductase reaction). Surprisingly, the experiments also showed that cells treated with Compactin responded by increasing endogenous levels of HMG-CoA reductase activity. When the rats were given Compactin repeatedly for 7 days, no decrease in cholesterol levels was observed. Strikingly, a single dose of Compactin in rats decreased the serum cholesterol levels between 3 to 8 hours. Later on, they found, that in rat system the effect of Compactin was counteracted by increased the amount of hepatic HMG-CoA reductase. This suggested that Compactin was not effective in rat system and as a result other animal systems were studied which revealed some interesting results. In hens, dogs and monkeys, the Compactin showed promising results by decreasing plasma cholesterol by 50% after one month. This indicated that Compactin can act as a new prototype in the list of cholesterol lowering drugs. Thereafter, the Sankyo Research Laboratories launched ‘Compact in Development Project’ in 1976, which was headed by Akira along with pathologists, pharmacologists, organic chemists, toxicologists, and microbiologists.

In collaboration with Akira Yamamoto, a physician at the Osaka University Hospital in Osaka, Sankyo conducted a Phase I and Phase II clinical trials in 1978, which reported significant efficacy and better safety profile of Compactin.
Unfortunately, the Compactin was withdrawn from market by Sankyo because at high doses (100 or 200 mg/kg/day) the dogs developed lymphoma during a period of 2 years.[9]

In 1979, Merck reported a statin named Mevinolin which was isolated from the fungus Aspergillus terreus.[12, 13] The Mevinolin was very similar to Compactin in chemical structure. During same year Akira isolated another statin i.e., Monacolin K from Monascus ruber.[14] Later on both of these Statins were found to be similar and renamed Lovastatin. The clinical benefits of Lovastatin in Mabuchi’s report stimulated Merck to conduct large-scale clinical trials in high risk patients and long-term toxicity studies in dogs. In 1986, Lovastatin was given FDA approval and Merck became the first company to commercialize Lovastatin. After Lovastatin, six other statins i.e., 2 semi-synthetic statins (pravastatin and simvastatin) and 4 synthetic statins (atorvastatin, fluvastatin, pitavastatin and rosuvastatin) have been commercialized.[15] It is estimated that around 30 million people worldwide are dependent on statins.

**Cholesterol and Its Association with Statins**

Since, the Statins were discovered; the cholesterol has been presented in a very negative and vague manner. The people have started avoiding foods that contain cholesterol. It is totally a myth that taking cholesterol rich foods are dangerous to your heart and vessels. In fact, studies show that the groups of people who had low levels of cholesterol in blood became atherosclerotic just like the people who had high blood cholesterol.[16]

Also, there is no conclusive evidence that supports the fact that too much animal fat and cholesterol in the diet promotes atherosclerosis or heart attacks. On contrary, sedentary habits, smoking, hypertensive and mentally stressed individuals were found to get more predisposed to high levels of cholesterol.[17]

The word cholesterol is derived from two Greek words – *chole* meaning *bile* and *-ol* meaning *alcohol*. It is a type of modified sterol that’s found in all cells of the body. Some of the major functions of cholesterol in body are:[18]

- To build and maintain cell membranes and increases membrane packing
- Limit the permeability of the plasma membrane to neutral solutes, sodium ions and hydrogen ions.
- Provide support to caveolae and clathrin-coated pits in lipid rafts for conducting signaling processes.
- Provide insulation in myelin sheath for more efficient conduction of impulses.
- Serve as precursor molecule for the synthesis of vitamin D and all steroid hormones
- Secreted along with bile juice helps in emulsification of fats in intestine and absorption of fat-soluble vitamins, A, D, E, and K.

The cholesterol is transported in the blood by lipoproteins namely Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), chylomicrons and chylomicrons remnants. These lipoproteins have a common structural feature which can be described as a central hydrophobic core surrounded by a hydrophilic membrane. The cholesterol esters and triglycerides form the hydrophobic core while as apolipoproteins, phospholipids and free cholesterol constitute hydrophilic membrane. Below is the Table 1 which describes the major properties of these lipoproteins[19]

| Lipoprotein       | Density (g/ml) | Size (nm) | Major lipids                              | Major apolipoproteins |
|-------------------|---------------|-----------|-------------------------------------------|-----------------------|
| Chylomicrons      | <0.930        | 75-1200   | Triglycerides                             | Apo B-48, Apo C, Apo E, Apo A-I, A-II, A-IV |
| Chylomicon Remnants | 0.930-1.006  | 30-80     | Triglycerides Cholesterol                 | Apo B-48, Apo E       |
| VLDL              | 0.930-1.006   | 30-80     | Triglycerides                              | Apo B-100, Apo E, Apo C |
| IDL               | 1.006-1.019   | 25-35     | Triglycerides Cholesterol                 | Apo B-100, Apo E, Apo C |
| LDL               | 1.019-1.063   | 18-25     | Cholesterol                               | Apo B-100             |
| HDL               | 1.063-1.210   | 5-12      | Cholesterol Phospholipids                 | Apo A-I, Apo A-II, Apo C, Apo E |

**Table 1**: Types of Lipoproteins and associated properties
From health perspective, doctors examine only LDL and HDL levels to conclude any risk towards atherosclerosis and cardiovascular disease (CVD). The cholesterol in LDL particles is sometimes referred as bad cholesterol because it serves as a raw material for cholesterol plaques in walls of arteries. Accumulation of cholesterol plaques in atherosclerosis can lead to cardiovascular diseases like coronary artery disease, cerebrovascular disease and peripheral arterial disease.\[20\]

Interestingly, LDL is the major transporter of cholesterol in the blood and LDL receptors provide a gateway to transport cholesterol within the cells. When this gateway gets disrupted, the LDL molecules can no longer be utilized by cells and wander in the blood, and in long run cause atherosclerosis. It appears from here that LDL as such is not bad as long as LDL receptors are functioning properly. In addition, it can also be argued that high level of LDL might serve as a marker for dysfunctional or low levels of LDL receptor. Worth to mention here, LDL is not just carrier of cholesterol but also serves as reservoir to transport fats, vitamin D and fat soluble antioxidants.\[21\] The cholesterol present in outer shell of LDL serves as a protective layer to prevent oxidation of fats in lipoproteins. Moreover, it has been found that LDL cholesterol also protects ApoB protein from attack of glucose or fructose. Indeed, it is the oxidized and glycated form of LDL molecules that have been found to accumulate at plaque sites and influence the diseases like diabetes.\[22\] The beneficial effects of LDL were further evident from the fact that low levels of LDL can escalate problems such as dementia and memory loss.\[23\] Earlier studies have also indicated that there exists a strong link between low LDL cholesterol levels and higher cancer risk.\[24\] Hence, all these studies indicate that LDL molecules are vital in certain biological processes and interfering with LDL synthesis by can limit bioavailability of essential nutrients to body cells. As statins work by lowering low density lipoprotein cholesterol, it is quite possible that patients taking statins might experience side effects or deficiencies which are outcome of cholesterol deficiency.

HDL (sometimes referred as good cholesterol) acts like a maintenance crew that removes excess cholesterol from cells, and recycles it back to liver, which secretes it in the form of bile salts. The antiatherogenic effect of HDL is determined by apo A-I component that induces cholesterol efflux from foam cell macrophages at atherogenic lesions.\[25\] HDL molecules also contain an enzyme known as paraoxonase, which protects the LDL molecules from oxidation.\[26\] There are several reports which document direct co-relation between the Statin therapy and increase in HDL levels.\[27, 28\] However, there is not enough evidence that sheds light on association of antiatherogenic properties of increasing HDL. A Meta analysis of Prospective Pravastatin Pooling Project, reported that there exists a negative association between HDL cholesterol and the risk of coronary artery disease death and myocardial infarction, both in placebo-treated patients and in Pravastatin-treated patients.\[29\] In yet another study named as Heart Protection Study, again a negative association was found between HDL cholesterol levels, HDL particle number, apoa-A-I levels and the risk of occlusive cardiovascular events; both placebo-treated individuals and simvastatin treated individuals.\[30\] It should be noted that there is not any conclusive data that shows significant association of statins with HDL cholesterol levels and CVD risk. In the Collaborative Atorvastatin Diabetes Study (CARDS), no significant change was observed in HDL cholesterol and apoa-A-I levels, and moreover neither any co-relation could be predicted for CVD risk in diabetic patients treated with atorvastatin.\[31\]

Several studies suggest that HDL cholesterol efflux capacities might serve as a better biomarker for atherosclerosis than HDL cholesterol levels. However, Khera et al. work on almost 100 patients treated with 10 mg atorvastatin, 40 mg Pravastatin or 80 mg atorvastatin for 16 weeks reported no effects of statin therapy on HDL.
cholesterol efflux capacities. Two transporters have been identified that play role in cholesterol efflux i.e., SR-B1 transporter utilized by antiatherogenic HDL particles and ABCA1 transporter utilized by pre-β-1 HDL. Upon treatment with statins like 40 mg rosuvastatin and 80 mg atorvastatin it was observed that pre-β-1 HDL levels decreased while as the large α-1 HDL particles increased. Likewise, in type 2 diabetic patients, treatment with atorvastatin lowered the amount of pre-β-1 HDL particles. This in-turn leads us to the fact that statin therapy on transporter-specific cholesterol efflux needs to be studied using more robust cellular models.

One of the major concerns that have challenged current therapeutic application of statins in clinical therapeutics is that few patients receiving statin therapy fail to respond to treatment or display statin tolerance. As a result they are subjected to high doses of statin to achieve desired therapeutic effect which predisposes them to adverse effects like brain diseases, liver injury, muscle pain & damage, type-2 diabetes etc. Here we will shed some light on those side effects of statins which are associated with cholesterol.

**Cholesterol, statin and brain disease:**

Cholesterol is found abundantly in the brain and constitutes almost 23% of total body cholesterol. One of the interesting facts about the brain cholesterol is that it is made locally and the blood brain barrier does not allow circulating body cholesterol to enter central nervous system (CNS). However, when the brain cholesterol gets hydroxylated to 24S-hydroxycholesterol by cytochrome P450 oxidase Cyp46a1, the latter form of cholesterol can easily cross blood brain barrier and get metabolized in liver. The importance of cholesterol in brain is supported by the fact that dyshomeostasis in cholesterol biosynthetic pathways causes’ number of inherited diseases (like Niemann-Pick type C disease, Lemli–Opitz syndrome, desmosterolosis, Rett syndrome, Huntington’s disease etc) and neurodegenerative diseases (like Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis etc). Most of the knowledge about a molecule is gained through experimental studies and following are some of studies which have dissected role of cholesterol in brain cells e.g., transgenic mice over-expressing Cyp46 displayed increased expression of synaptic proteins and improved spatial memory, cholesterol depletion impairs synaptic vesicle exocytosis in cultured neurons; cholesterol depletion impairs endocytosis due to destabilization surface AMPA receptors; cholesterol depletion impairs long-term potentiation due to destabilization surface NMDA receptors etc.

The therapeutic application of Statins for the treatment of neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease, ischemic strokes multiple sclerosis and traumatic brain injury has shown some controversial results. The LEADe (Lipitor’s Effect in Alzheimer’s Dementia) study showed that 80 mg atorvastatin had no effect on mild to moderate AD patients. Likewise, the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study reported no effect on cognition in patients given pravastatin or placebo for a period of 3.5 years. There is however randomized clinical trials wherein it was found that 10 or 40 mg of simvastatin for 6 months and 20 mg lovastatin for 6 months resulted in cognition impairment. A study on mice also showed that administration of atorvastatin orally for long-term precipitated alterations in behavior and cognition. Depending upon the medical history of patient, studies show that statins reduced the risks of ischemic strokes but worsened the risk of hemorrhagic strokes. Other studies suggest that statins can precipitate neuropathy like symptoms in patients on statins. It is generally presumed that chemical structure of statins can be cause behind the controversial results. Lipophilic statins can easily cross the blood brain barrier and directly affect brain cholesterol levels.

**Cholesterol, statin and liver:** Liver plays a vital role in regulating cholesterol levels within body through two ways: one by synthesizing cholesterol...
which is transported to body cells by lipoproteins and other by sequestering cholesterol from body in the form of bile salts. The incidence of statin induced liver injury is very low (almost 1%) and the reported abnormalities include hepatitis (when transaminase level is greater than 3 times the upper limit of normal), autoimmune hepatitis–like syndrome (presence of autoantibodies like antinuclear antibody and antismooth muscle antibody), cholestatic pattern associated with jaundice.\textsuperscript{[47]} Meta-analyses of randomized placebo controlled trials reported that there occurred no significant increase in liver enzymes like alanine transaminase at mild to moderate dosage. Two retrospective studies showed that statin therapy did not affect liver enzyme levels in patients suffering from steatohepatitis and nonalcoholic fatty liver disease compared with patients not taking statins.\textsuperscript{[48]} A study was conducted over a 5-year period which included 23,000 patients on statins. It was found that only 0.1% patients had severe ALT levels and most importantly severity was associated with drug-drug interactions.\textsuperscript{[49]} Below Table 2 describes the relation between statins and liver abnormalities\textsuperscript{[48]}

| Table 2: Meta-analyses on long-term statin treatment and liver toxicity |
|-----------------------------------------------|
| Meta-analysis    | Number of studies | Total of subjects | Age (years) | Exposure to study medication | Treatment type and dosage (mg/day) | Liver function tests abnormalities | Conclusions |
| PPP Project      | 3                | 19.768            | 21–75      | >5 years                      | Pravastatin 40                      | Pravastatin: Placebo: 1.0%         | Pravastatin was well tolerated, with no excess of liver function abnormalities |
| de Denus S       | 13               | 49.275            | 55–75      | From 48 weeks to 6.1 years    | Pravastatin 40 Simvastatin 30–45 Simvastatin 27–30 Fluvastatin 40–80 | Statins: Placebo 1.05%             | Only fluvastatin was associated with a significant increase in the odds of having liver function tests abnormalities (1.13% vs. 0.29%) |
| Alsheikh-Ali AA  | 23               | 75.317            | 55–75      | From 0.9 to 6.1 years         | Lovastatin 20–80 Simvastatin 10–80 Pravastatin 40 Fluvastatin 80 | High-dose: 271; Low-dose: 114 (per 100,000 person-years for each 10% reduction in LDL-C) Drug- and dose-specific effects are more important determinants of liver toxicity than magnitude of LDL-C lowering |
| Dale KM          | 9                | 21.765            | 48–64      | From 1 to 5 years             | High dose: 80 Atorvastatin 20–80 Simvastatin 40–80 Lovastatin 76 Low dose: 80 Simvastatin 20–40 Pravastatin 40 Atorvastatin 10 Lovastatin 4 | High-dose statin: 1.5%; Low-dose statin: 0.4% Higher intensity statin therapy significantly increases the incidence of transaminase elevation in higher intensity hydrophilic statins group |

Taking into account the anti-inflammatory and anti-thrombotic effects property of statins, it is believed that statins may exert beneficial effects in reducing liver cancer, decreasing fibrosis or fatty deposition and improvement of portal hypertension. In a recent Cochrane meta-analysis, statins were found to improve serum aminotransferase levels in NAFLD and NASH; however no effect was observed on histological level and liver-related mortality and morbidity.\textsuperscript{[48]} Cholesterol, statins and steroid hormones:

There are three classes of steroid hormones in mammals namely glucocorticoids, mineralocorticoids, and adrenal androgens. These can be further categorized as adrenal steroid hormones (like cortisol, aldosterone and DHEA(s)) and non-adrenal steroid hormones (like testosterone, progesterone and estradiol). The precursor for all these steroid hormones is cholesterol contained in low density lipoproteins. So theoretically speaking, statins should produce profound effect on steroid levels. However, upcoming reports show that statins do not alter the steroid hormones to the extent as expected. A
Clinical report with Parvastatin showed that although total and LDL cholesterol decreased however there was no significant affect on levels of steroid hormones or gonadotropins.[50] Similarly, no change in androgens or estrogens was observed in postmenopausal women in presence or absence of statin.[51] Schooling et al. reported through meta-analysis of randomized controlled studies which involved both men and women that statins like rosuvastatin led to moderate decline in plasma testosterone levels. On contrary, the plasma levels of gonadotropin and ACTH showed a significant increase followed by no change in dehydroepiandrosterone sulphate and cortisol.[52] A Cross-sectional study within the prospective population-based Rotterdam Study revealed that statins significantly decreased serum total and non-SHBG-bound testosterone levels.[53] Additionally, a study conducted in mice showed that Simvastatin treatment did not alter cholesterol levels but aggravated the glucocorticoid insufficiency associated with hypocholesterolemia.[54]

**Cholesterol, statins and Vitamin D:** The cholesterol also acts as a precursor for biosynthesis of vitamin D. In the presence of UV radiation 7-Dehydrocholesterol gets converts into cholecalciferol--vitamin D3 in the human skin.[55] Vitamin D is very well known for calcium metabolism and upcoming reports have found many more important roles like blood sugar regulation, mental health, the immune system regulation and cancer prevention.[56] Thus, it will not be wrong to say that statin might alter the vitamin D levels and the functions associated. Surprisingly, randomized study showed that rosvastatin, atorvastatin, simvastatin and lovastatin led to a significant rise in 25-hydroxy vitamin D levels.[57] In contrast, fluvastatin had no significant affect on vitamin D levels. The effect of vitamin D on statins is quite interesting. A study claimed that patients which received vitamin D (800 IU/day) along with atorvastatin had apparently lower levels of total and LDL cholesterol as compared to patients on atorvastatin alone. Strikingly, vitamin D decreased the plasma levels of atorvastatin by 10%.[58] Only one study claimed that statin decreased vitamin D levels by 21.4% in patients aged 60 and older.[59] So far, evidence regarding the association of statin and vitamin D has remained inconclusive due limited data and conflicting results. Further randomized controlled trials are warranted to make a direct correlation.

**Conclusion**

In conclusion we believe that a multicentered, placebo controlled, randomized and double blinded trial with a large population should be addressed to establish the risks associated with statins. One of the major concerns which physicians should consider about statins is tolerability and safety during their clinical use and clinicians should pay attention to it if encountered and respond reasonably and quickly. The pharmacokinetic and pharmacodynamic properties of the statins should be carefully assessed to elucidate drug interactions and safety profile in patients with hypercholesterolemia who are require long-term therapy. Overall, emphasis should be laid on risk-benefit balance of statin during treatment.

**Financial support and sponsorship**

Nil

**Conflicts of interest**

There are no conflicts of interest.

**Contribution:** *The authors have contributed equally.

**References**

1. Stancu C, Sima AJ. Statins: mechanism of action and effects. Cell Mol Med 2001; 5:378-87.

2. Stone NJ et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. American
College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129:S1-45.

3. Davidson MH. Controversy surrounding the safety of cerivastatin. Expert Opin Drug Saf 2002;1:207-12.

4. Bloch K. Summing up. Annu. Rev. Biochem 1987); 56: 1–19.

5. Daniel S, Joel A, Eugene B. Feigelson. Effects of triparanol (mer-29) on cholesterol biosynthesis and on blood sterol levels in man. J Clin Invest 1961; 40: 884–893.

6. Carlson LA. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. J Intern Med 2005;258:94-114.

7. Fanny L, Bart S. Fibrates, glitazones, and peroxisome proliferator-activated receptors. Arterioscler Thromb Vasc Biol 2010; 30: 894–899.

8. Kohzo A, Yoshimasa A, Toshihiko I. Role of bile acid sequestrants in the treatment of type 2 diabetes. World J Diabetes 2010; 1: 146–152.

9. Endo A. A historical perspective on the discovery of statins. Proc Jpn Acad Ser B Phys Biol Sci 2010; 86: 484–493.

10. Endo A, Kuroda M, Tsujita Y. ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterologenesis produced by Penicillium citrinum. J Antibiotics 1976; 29:1346–1348

11. Michael SB, Joseph LG. A tribute to Akira Endo, discoverer of a “Penicillin” for cholesterol. Atherosclerosis 2004; 5: 13–16.

12. Endo A. A historical perspective on the discovery of statins. Proc Jpn Acad. Ser B Phys Biol Sci 2010; 86: 484–493.

13. Bizukojc M, Ledakowicz S. A macrokinetic modelling of the biosynthesis of lovastatin by Aspergillus terreus. J Biotechnol 2007; 130: 422–435.

14. Goswami S, Vidyarthi AS, Bhunia B, Mandal T. A review on lovastatin and its production. J Biochem Tech 2012; 4: 581-587.

15. Peter HJ. Comparing HMG-CoA Reductase Inhibitors. Clin Cardiol 2003; 26:15-20.

16. Ravnskov U. Is atherosclerosis caused by high cholesterol? QJM: An Int Journal of Med 2002; 95: 397-403.

17. Nicola M, Gabriele G, Stefano PC, Javier F, Federico M, Giulio A. Anxiety, Stress-Related Factors, and Blood Pressure in Young Adults. Front Psychol 2016; 7: 1682.

18. Ira T. Cholesterol in health and disease. J Clin Invest 2002; 110: 583-590.

19. Kenneth RF, Carl G. Introduction to Lipids and Lipoproteins. Endotext book [Internet].

20. Brian A 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. European Heart Journal 2017; 38: 2459-2472.

21. Wadhera RK, Steen DL, Khan I, Giugliano RP, Foody JM. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. J Clin Lipidol 2016; 10: 472-89.

22. Fernandez-Ruiz I. Atherosclerosis: Should we redefine the normal LDL cholesterol range? Nat Rev Cardiol 2018; 15: 68-69.

23. Low levels of good cholesterol linked to memory loss, dementia risk. American Heart Association. ScienceDaily, 1 July 2008.

24. Low LDL cholesterol is related to cancer risk. American College of Cardiology. ScienceDaily, 26 March 2012.

25. Esin E, Necat Y, Ozgur A. High Density Lipoprotein and it’s Dysfunction. Open Biochem J 2012; 6: 78-93.

26. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La-Du BN. Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 1998; 101: 1581-1590.
27. Philip JB, Gunnar B, Mike KP, Stephen JN. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. J Lipid Res 2010; 51: 1546-1553.

28. Fergus MT, Peter J. Effects of Statins on High-Density Lipoproteins: A Potential Contribution to Cardiovascular Benefit. Cardiovasc Drugs Ther 2008; 22: 321-338.

29. Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM, Keech A, Packard C, Simes J, Byington R, Furberg CD. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. Circulation 2000; 102: 1893-900.

30. van Capelleveen JC et al. Association of High-Density Lipoprotein-Cholesterol Versus Apolipoprotein A-I With Risk of Coronary Heart Disease: The European Prospective Investigation Into Cancer-Norfolk Prospective Population Study, the Atherosclerosis Risk in Communities Study, and the Women's Health Study. J Am Heart Assoc 2017; 6: e006636.

31. Boekholdt SM. Levels and changes of HDL cholesterol and apolipoprotein A-I in relation to risk of cardiovascular events among statin-treated patients; a meta-analysis. Circulation 2013; 128: 1504-12.

32. Khera AV, Cuchel M, De LL-M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH, Rader DJ. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med 2011; 364: 127-135.

33. Ernst JS, Bela FA. Statins, cholesteryl ester transfer protein inhibition, high density lipoprotein particle metabolism and heart disease risk reduction. http://www.athero.org/commentaries/comm519.pdf.

34. Dallinga-Thie GM, van Tol A, Dullaart RP. Plasma pre beta-HDL formation is decreased by atorvastatin treatment in type 2 diabetes mellitus: Role of phospholipid transfer protein. Biochim Biophys Acta 2009; 1791: 714-8.

35. Juan Z, Qiang L. Cholesterol metabolism and homeostasis in the brain. Protein Cell 2015; 6: 254–264.

36. Lange Y, Ye J, Strebel F. Movement of 25-hydroxycholesterol from the plasma membrane to the rough endoplasmic reticulum in cultured hepatoma cells. J Lipid Res 1995; 36: 1092-7.

37. Anchisi L, Dessi S, Pani A, Mandas A. Cholesterol homeostasis: a key to prevent or slow down neurodegeneration. Front Physiol 2013; 3: 486.

38. Maioli S, Båvner A, Ali Z, Heverin M, Ismail MA, Puerta E, Olin M, Saeed A, Shafaati M, Parini P, Cedazo-Minguez A, Bjorkhem I. Is It Possible to Improve Memory Function by Upregulation of the Cholesterol 24S-Hydroxylase (CYP46A1) in the Brain. PLoS One 2013;8 :e68534.

39. Hering H, Lin CC, Sheng M. Lipid Rafts in the Maintenance of Synapses, Dendritic Spines, and Surface AMPA Receptor Stability. J Neurosci 2003; 23: 3262-71.

40. Martin MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: sometimes determinant and frequently implicated. EMBO Rep 2014; 15: 1036-52.

41. Jones RW, Kivipelto M, Feldman H, Sparks L, Doody R, Waters DD, Hey-Hadavi J, Breazna A, Schindler RJ, Ramos H. The Atorvastatin/Donepezil in Alzheimer's Disease Study (LEADe): design and baseline characteristics. Alzheimers Dement 2008; 4: 145-53.

42. Ford I et al. A Prospective Study of Pravastatin in the Elderly at Risk (PROSPER): Screening Experience and Baseline Characteristics. Curr Control Trials Cardiovasc Med 2002; 3: 8.
43. Bitzur R. Remembering Statins: Do Statins Have Adverse Cognitive Effects? Diabetes Care. 2016; 39: S253-9.
44. Schilling JM, Cui W, Godoy JC, Risbrough VB, Niesman IR, Roth DM, Patel PM, Drummond JC, Patel HH, Zemljic-Harpf AE, Head BP. Long-term atorvastatin treatment leads to alterations in behavior, cognition, and hippocampal biochemistry. Behav Brain Res 2014; 267: 6–11.
45. Scheitz JF, MacIsaac RL, Abdul-Rahim AH, Siegerink B, Bath PM, Endres M, Lees KR, Nolte CH. Statins and risk of poststroke hemorrhagic complications. Neurology 2016; 86: 1590-6.
46. Brenton W. The implications of statin induced peripheral neuropathy. J Foot Ankle Res 2011; 4: P57.
47. Manish T, Mark WR, Herbert LB. Statins and Liver Injury. Gastroenterol Hepatol (N Y). 2013; 9: 605-606.
48. Pastori D, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. Dig Liver Dis 2015; 47: 4-11.
49. Rossana MC, Luigi XC, Ronald BG, Eugene RSchiff. Statins in the Treatment of Dyslipidemia in the Presence of Elevated Liver Aminotransferase Levels: A Therapeutic Dilemma. Mayo Clin Proc 2010; 85: 349-356.
50. Bohm M, Herrmann W, Wassmann S, Laufs U, Nickenig G. Does statin therapy influence steroid hormone synthesis? Z Kardiol 2004; 93: 43-8.
51. Peck A, Chaikittisilpa S, Mirzaei R, Wang J, Mack WJ, Hodis HN, Stanczyk FZ. Effect of statins on estrogen and androgen levels in postmenopausal women treated with estrogen. Climacteric 2011; 14: 49-53.
52. Krysiak R, Okopien B. The effect of aggressive rosuvastatin treatment on steroid hormone production in men with coronary artery disease. Basic Clin Pharmacol Toxicol 2014; 114: 330-5.
53. Keyser CE, Lima FV, Jong FH, Hofman A, Rijke YB, Uitterlinden AG, Visser LE, Stricker BH. Use of statins is associated with lower serum total and non-sex hormone-binding globulin-bound testosterone levels in male participants of the Rotterdam Study. Eur J Endocrinol 2015; 173: 155-65.
54. Ouweneel AB, van der Sluis RJ, Nahon JE, Van Eck M, Hoekstra M. Simvastatin treatment aggravates the glucocorticoid insufficiency associated with hypocholesterolemia in mice. Atherosclerosis 2017; 261: 99-104.
55. Matthias W, Michael F. Holick. Sunlight and Vitamin D. A global perspective for health. Dermatoendocrinol 2013; 5: 51–108.
56. Rathish N, Arun M. Vitamin D: The “sunshine” vitamin. J Pharmacol Pharmacother 2012; 3: 118–126.
57. Miao H. Safety of statins: an update. Ther Adv Drug Saf 2012; 3: 133–144.
58. Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. Clin Pharmacol Ther 2009; 85: 198-203.
59. Bischoff-Ferrari HA, Fischer K, Orav EJ, Dawson-Hughes B, Meyer U, Chocano-Bedoya PO, Meyer OW, Ernst R, Schietzel S, Eberli F, Staehelin HB, Frey斯塔tė G, Roas S, Theiler R, Egli A, Wilson NM. Statin Use and 25-Hydroxyvitamin D Blood Level Response to Vitamin D Treatment of Older Adults. J Am Geriatr Soc 2017; 65: 1267-1273.