Review Article

A Global Review Article on Hyperlipidemia

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ABSTRACT

Hyperlipidemia is a medical condition characterized by an increase in one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters, phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein along with reduced high-density lipoprotein levels. This elevation of plasma lipids is among the leading risk factors associated with cardiovascular diseases. Introduction, type of lipoprotein, classification of hyperlipidemia, Complications of hyperlipidaemia, causes; Symptoms of hypelipedemia, Pathogenesis of hyperlipidemia, Pathogenesis of hyperlipidemia, diagnosis, prevention, treatments.

Keywords: Hyper lipidemia,cholesterol, Fibrates , statins.

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INTRODUCTION

Hyperlipidemia is outlined as an elevation of one or more of the following: cholesterol, cholesterol esters, phospholipids, or triglycerides. Abnormalities of plasma lipids can result in predisposition to coronary, cerebrovascular, and peripheral vascular arterial diseases.[1,2] The hyperlipidemia is traditionally defined as conditions in which the concentration of cholesterol or triglyceride-carrying lipoproteins in plasma exceeds an arbitrary normal limit.[3,4] Liver is to blame for dominant the content of cholesterin with in the blood stream. In the body, liver produces roughly 80% of the cholesterol whereas rest of the cholesterol is obtained from the food like fish, eggs, meat[5,6.] Hyperlipidemia is considered one of the major risk factors causing to cardiovascular diseases (CVDs). CVDs accounts for 1/3 rd of total deaths around the total world, it is believed that Cardiovascular diseases will turn out to be the main cause of death and incapacity worldwide by the year 2020[7-9]. Meanwhile, statins and fibrates stay the many enemy of hyperlipidemic specialists for the treatment of raised plasma sterol and triglycerides individually, with the value of most symptoms on the muscles and also the liver.[10]

TYPES OF LIPO PROTEINS

Chylomicrons (CM),

Verylow-densitylipoproteins (VLDL),

Low-density lipoproteins (LDL),

Intermediate-density lipoproteins (IDL)

High-densitylipoproteins (HDL)[11]

Chylomicrons

These are the largest particles both in size as well as in density, and its concentration is directly correlated with dietary triglyceride content.

VLDL:

Very low-density lipoproteins are smaller particles carrying more chylomicronsthan triglyceides, and are secreted from the liver. Very low density lipoprotein carries sterol from the liver to organ and tissues in the body. They are formed from the mixture of cholesterol and triglycerides.[12]

IDL:

VLDL particles after lysis by lipase enzyme in the capillaries of adipose tissue and muscle give rise to intermediate density lipoprotein.

LDL:

According to Lee et al., and Galeanoet al., low-density lipoproteins are synthesised partly in intestinal chyle and partly after lipolysis of very low density lipopoteins. It is directly correlative to CHD.

HDL:

HDL is commonly referred as good cholesterol. High-density lipoproteins are synthesized in the liver. It carries cholesterol and other lipids from tissues back to the liver for degradation. HDL plays an antiatherogenic role.[13]

CLASSIFICATION OF HYPELIPIDEMIA

On the idea of lipid type

Hypercholesterolemia-In this the level of cholesterol is elevated.

Hypertriglyceridemia-It is outlined as level of triglycerides elevated.

On the idea of causing factor (fig.1)

***3.1. Primary (*Familial:** hyperlipidemia**)**

it is also called familial due to a genetic defect, it may be monogenic: a single gene defect or polygenic: multiple gene defects. Primary hyperlipaemia can usually be resolved into one of the abnormal lipoprotein pattern summarized.

Type I–Raised cholesterol with high triglyceride levels.

Type II–High cholesterol with normal triglyceride levels.

Type III–Raised cholesterol and triglycerides.

Type IV–Raised triglycerides, atheroma and uric acid.

Type V–Raised triglycerides

***3.2. Secondary (*Acquired hyperlipidemia)**

It is acquired because it is caused by another disorder like diabetes, glomeular syndrome, chronic alcohol intake, hypothyroidism and with use of drugs like corticosteroids, beta blockers and oral contraceptives. Secondary hyperlipidemia combined with significant hyper triglyceridemia can cause pancreatitis.[15]

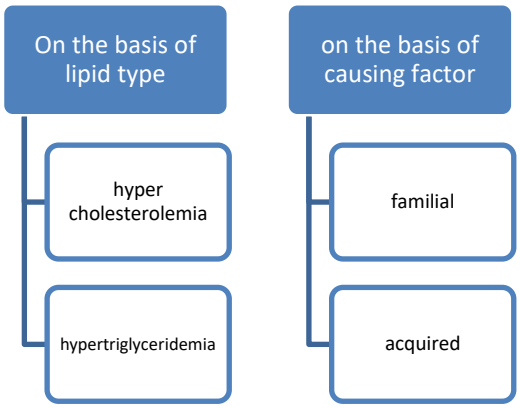

Figure 1: Idea of causing factor

COMPLICATIONS OF HYPERLIPIDEMIA

Atheosclerosis

Hyperlipidemia is the major risk factor for atherosclerosis, which is the major cause of cardiovascular disease. Atherosclerosis a pathologic process characterized by the accumulation of lipids, cholesterol and calcium and the development of fibrous plaques within the walls of large and medium arteries.[16]

Coronary Artery Disease

Atherosclerosis, the major cause of coronary artery disease, characterized by the accumulation of excess lipid and the formation of fibrous plaques within the wall of the arteries resulting in narrowing of the arteries that supply blood to the myocardium, and results in limiting blood flow and insufficient amounts of oxygen to meet the needs of the heart.[17]

Myocadial Infraction

MI is a condition which occurs when blood and oxygen supplies are partially or completely blocked from flowing in one or more cardiac arteries, leads to damage or death of heart cells. The occlusion may be due to ruptured atherosclerotic plaque.[18]

Ischemic stroke or cerebrovascular accident

Stroke is the fourth leading cause of death. Usually strokes appear due to blockage of an artery by a blood clot or a piece of atherosclerotic block that breaks loose in a small vessel within the brain. Many clinical trials revealed that reducing of low-density lipoprotein and total cholesterol by 15% significantly reduced the risk of the first stroke[19].

CAUSES

Sterol, fatty acids, trans fat in the following food may increase the lipid level in blood:

- Dairy products.
- Ice cream pastries.
- Fried and junk foods.
- Meat etc.[20]

Other disorders like obesity, diabetes mellitus and hypothyroidism is major causes for hyperlipidemia. Smoking and low exercising may lead to hyperlipidemia[21].Excessive use of alcohol also increases the risk of hyperlipidemia. Certain drugs as steroids and β–blockers may cause hyperlipidemia (3) Lipoprotein lipase mutations[22].

Several other causes of hyperlipidemia

- Obesity.
- Genetic or inheritance.
- Smoking.
- Several drugs such as corticosteroids, estrogen, betablockers may risk for hypertriglyceridemia.
- Alcohol, steroids, hypothyroidism, kidney failure etc.
- Low exercise [23]

SYMPTOMS OF HYPERLIPIDEMIA

Hyperlipidemia usually has no noticeable symptoms and tends to be discovered during routine examination for atherosclerotic cardiovascular disease [24]

•chest pain (angina), heart attack or stroke.

• When levels are exceed high, cholesterol may be deposited in tendons or just beneath the skin under the eyes.

• liver, spleen or pancreas are swelled .

• blood vessels block in brain and heart.

• Higher rate of obesity and glucose intolerance.

• Pimple like lesions across the body[25]

PATHOGENESIS OF HYPERLIPIDEMIA

During the early stages of the hyperlipidemia, blood monocytes and platelets attach to a vessel wall at the sites of endothelial damage. The release of the mediators such as platelet derived from growth factors leads to a growing of smooth cells in the intimal and medial lining of the vessel, collagen synthesis, cholesterol uptake and the initialfor the hyperlipidemic plaque results. Plaque ruptures are resulting in the acute syndromes of unstable angina, myocardial infarction and sudden cardiac death [26.]

SIGNIFICANCE

Health care providers are concerned about hyperlipidemia because of the well established association between lipid concentrations and the risk of CVD, the leading cause of death in the United States.[27-29]A landmark study that helped establish that therapeutic interventions to lower cholesterol levels result in reduced risk of cardiovascular morbidity or mortality was the Lipid Research Clinics Coronary Primary Prevention Trial, which was published in two parts (each using a different statistical analysis) in 1984.[30,31]A complete history information of the cholesterol controversy can be found in a multi-part review (available on line) which was published over a 3 year span in the Journal of Lipid Research.[32-38]

DIAGNOSIS

No any other specific symptom for Hyperlipidemia it can be only detected by a blood test. Screening for hyperlipidemia is done with a blood test called a lipid profile.[39]Hyperlipidemia may be diagnosed by a regular checkup of LDL, HDL, VLDL and Triglycerides in blood test.[40]

PREVENTION OF HYPERLIPIDEMIA

• Low fatty acid and cholesterol diet should be taken.

• Intake of foods high in soluble fiber such as oats, beans and certain fruits.

• Exercise regularly to maintain a healthy weight.[3]

TREATMENT

The following lifestyle modification may lower the cholesterol level:

- Proper diet.
- Less weight of the body.
- Regular exercise.
- Having non-oily food.
- Eat pears, apples, bananas etc.
- Have fish twice a week.
- Maximum time the lifelong treatment and medications are required
- Fibrates (fenofibrate), statins may lower the triglyceride levels[40]

TEATMENTS

Therapeutic lifestyle changes

Diet changes, regular physical exercise, smoking cessation, and weight reducing should be tried as initial treatment, especially in mild cases of hyperlipidemia and in persons without CHD or CHD risk equivalent and<2 risk factors. It should be kept in mind that when dieting, cholesterol intake is reduced. At the same time, production of cholesterol, especially by the liver, increases.[3]It is recommended that the intake should be restricted to 25%-35% of energy intake and that saturated fatty acids make up less than 7% of energy intake and that cholesterol intake should be less than 200 mg daily. The intake of plant sterol esters and soluble fibre is pefered.[3]

Ayurvedic treatment

Ayurvedic medicine is one of the world's earlier medical systems. Ayurvedic therapeutics is based on the "laws" of nature. Its approach to health-care is based on understanding the interrelationship of body, mind and spirit. The aim of ayurveda medicine is to integrate and balance these elements to prevent illness and promote health through diet, nutrition, herbs, yoga, meditation and daily seasonal routines[41].

Home medications

In other hand, pharmacological and ayurvedic treatment, some home remedies are also beneficial in the treatment of hyperlipidemic Nuts; Almonds lower LDL by 4.4%, Walnuts lower LDL by 16%.

Oatmeal; Drops LDL by 12-24%.

Orange juice ; Reduce blood cholesterol level.

Coriander seeds; Lower cholesterol and triglycerides levels.

Fish oil; Lower triglycerides levels.

Honey ; Lower cholesterol level.

Soyabeans ; Lower the production of new cholesterol.

Indian Gooseberry; decrease the excess cholesterol build-up.

Brown Rice ; Lower cholesterol level.

Turmeric ; Lowers LDL cholesterol levels.

Brinjal ; Lowers LDL cholesterol levels.

Coconut oil ; Increases HDL and improves the LDL/HDL ratio.

Fenugreek seeds; Lowers cholesterol level by 14%[3]

Plants having hypolipidemic activity

Medicinal plants have always been considered as a healthy source of life for all people due to its rich therapeutic properties and being 100% natural [43.] Over the past decade, herbal medicine has become a topic of global significance, making an impact on both world health and international trade. Regular usage of herbal medicine by a large proportion in the developing countries is largely due to the high cost of Western Pharmaceuticals and Healthcare [43.]

PHARMACOLOGICAL TREATMENT

Lot of hypolipidemic drugs are available in the market for the treatment of hyperlipidemia. Drug Project indicating that the drugs are relatively ineffective for preventing myocardial infarction in patients with pre established CHD.[44]

Drug therapy

Increase LDL, the presence of risk factors, and documentation of CHD should qualify developing drug therapy along with TLC. Current lipid-lowering drugs include statins, ezetimibe, bile acid sequestrants or bile binding resins, niacin, fibric acid derivatives, and plant sterols. Medication specially designed to lower blood cholesterol levels may be prescribed when dietary modifications prove inadequate.[45]

Fibric acid derivatives (Fibrates)

Fibrates include clofibrate, gemfibrozil, fenofibrate, and bezafibrate, are a widely used class of antihyperlipidemic agents, results in a significant reduction in plasma triglycerides and a modest reduction in LDL sterols. HDL cholesterol level increases moderately. Angiographic experimental results showed that fibrates play an maximum role in slowing the development of coronary atherosclerosis and lowering the occurrence of coronary artery disease.

Mechanism of action

Data from studies in rodents and in humans imply 4 main mechanisms of fibrates:

Stimulation of lipoprotein lipolysis

Fibrates acts primarily as ligands for the nuclear transcription receptor, PPAR-α. They elevate the expression of lipoprotein lipase, apo, and down-regulate apo C-III, an inhibitor of lipolysis. Fibrates also elevated the level of HDL cholesterol by enhancing the expression of apo AI and apo AII.[7]

Enhancing hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production.

Fibrates increase the formation of fatty acid transport protein and acyl-CoA synthetase, which contribute to the increase uptake of fatty acid by the liver and also a result in a lower accessible of fatty acids for triglyceride formation.

Increase removal of LDL particles.

Fibrates, appears to elevated LDL catabolism via the receptor-mediated pathway; LDL particles became major and more lipid high level and therefore had more affinity for receptors.

Increase in HDL formation and stimulation of reverse cholesterol transport.

Fibrates enhance apo A-I formation in the liver which leads to the observed elevation in plasma levels of apo A4 and HDL-cholesterol and a more effective for reverse cholesterol transport.[5]

Nicotinic acid derivatives (Niacin)

Niacinis, a water-soluble vitamin of type B, is the earliest lipid reducing agent used to treat hyperlipidemia and proved to decrease cardiovascular morbidity and total mortality. It reduces the total cholesterol, LDL cholesterol, triglycerides[5]

Mechanism of action

Niacin inhibits hormone-sensitive lipase which decreases triglycerides lipid lysis the main producer of circulating free fatty acids. The liver usually used for these circulating fatty acids as a major lead role for triacylglycerol formation. Therefore, niacin inhibits VLDL secretion, in turn lower the production of LDL.[5]

Side effects

Niacin treatment has been plagued by low patients compliance rates. The most common side effects are intense cutaneous flush which affect more than three quarters of patients, itching, headache and some patients experience nausea and abdominal discomfort. Niacin also elevates liver enzymes[45]

Selective cholesterol absorption inhibitor (Ezetimibe)

The discovery and development of ezetimibe, the first member of a group of drugs that inhibit intestinal absorption of phytosterols and cholesterol, has improved the treatment of hypercholesterolemia. It inhibits the absorption of sterol from the small intestine no any effect on the plasma concentrations of the vitamins ADEK

Mechanism of action

Ezetimibe selectively inhibits absorption of cholesterol in the small intestine, leading to a lower in the delivery of intestinal cholesterol to the liver by blocking the Niemann–Pick C1-like 1 protein (NPC1L1), a human sterol transport protein. This causes an increase in the clearance of sterol from the blood stream.

Side effects

Ezetimibe is usually well tolerated drug; the most common side effects include headache, abdominal pain and diarrhea. Ezetimibe appears to cause elevations in liver

function tests include elevations in alanine transaminase and aspartate transaminase.[7]

NEW POTENTIAL TARGETS AND TREATMENTS

Recently, many clinical trials revealed new potential agents with promising antihyperlipidemic activity.

Acyl-CoA cholesterol acyl transferase inhibitors(ACAT)

Acyl-CoA cholesterol acyl transferase (ACAT) is the enzyme that catalyzes the transform of intracellular cholesterol into cholesteryl esters. ACAT has two isomers, termed ACAT1 and ACAT2.

Microsomal triglyceride transfer protein (MTP) inhibitors

Microsomal triglyceride transfer protein (MTP) has multiple functions including transferring neutral lipids between membrane vesicles, the biosynthesis of CD1, antigen-presenting molecules, as well as in the regulation of cholesterol ester biosynthesis.

Cholesteryl ester transfer protein (CETP)inhibitors

CETP in liver facilitates the shift of cholesteryl esters from anti-atherogenic HDLs to proatherogenicapo lipo protein B containing lipoproteins, including VLDLs and LDLs. Furthermore, most studies showed that there is evidence that CETP may play a proatherogenic role by involving in reverse cholesterol transport and support the idea that inhibition of CETP slows the progress of atherosclerosis.[7]

Squalene synthase inhibitors

Squalene synthase (SqS) catalyzes farnesyl pyrophosphate to formation of squalene, Catalysis by SqS is the first committed step in sterol synthesis, and one of these sterols is cholesterol.[5]

Hydroxymethylglutaryl-CoA synthase inhibitors

HMG synthase catalyzes the chemical reaction that turn acetyl-CoA and acetoacetyl CoA to 3-hydroxy-3-methylglutaryl-CoA.

ATP citrate lyase inhibitors

ATP citrate lyase (ACL)is the primary enzyme accountable for the synthesis of cytosolicacetyl-CoA and oxaloacetate. Synthesis of cytosolicacetyl-CoA and oxaloacetate represent to an important step in the synthesis of fatty acids and cholesterol. For this reason, inhibition of ACL is a promising strategy in the treatment of dyslipidemia.

Acyl coenzyme A: diacyl glycerol acyltransferase (DGAT)

DGAT is a microsomal enzyme that joins Acyl CoA to 1,2-diacylglycerol in the final step in triglyceride bio synthesis.

Squalene epoxidase inhibitors

Squalene epoxidase is one of the rate controlling enzymes for the first oxygenation step in sterol bio synthesis.

Lanosterol synthase inhibitors

lanosterol synthase (LSS) Catalyzes the cyclization of (S)-2,3 oxidosqualene to lanosterol, the initial sterol between in the cholesterol synthesis pathway.[7]

RECENT DRUG FOR HYPERLIPIDEMICS

The FDA has approved two new non-**statin drugs** that clinical trials indicated can help reduce high cholesterol. **Nexletol and Nexlizet** can be used with statins that have modulate or minimal side effects. The two new drugs have some side effects different from those associated with statins.[46]

CONCLUSION

From the above study the hypelipdemia condition is major risk factor for cardiac disease. hypelipidemia can be treated by recent drugs and diet food chart, home remedies, regular physical exercise. If attentive care is given to diet maintenance and fitness may reduce the risk of hyperlipidemic, CVD and many other disease.

REFERENCES

1. Mishra PR, Panda PK, Apanna KC, Panigrahi S. Evaluation of acute hypolipidemic activity of different plant extracts in Triton WR-1339 induced hyperlipidemia in albino rats. Pharmacologyonline. 2011;3:925-34. Doi: https://pharmacologyonline.silae.it/files/archives/2011/vol3/098.mishra.pdf

2. DiPiro JT. Pharmacotherapy handbook. Wells BG, Schwinghammer TL, DiPiro CV, Education MH, editors. Appleton & Lange; 2000 Jan.

3. Verma, N. INTRODUCTION TO HYPERLIPIDEMIA AND ITS TREATMENT: A REVIEW. *International Journal of Current Pharmaceutical Research*, 2016;*9*(1):6-14. Doi: https://doi.org/10.22159/ijcpr.2017v9i1.16616.

4. Goodman LS, Gilman A. The pharmacological basis of therapeutics. Macmillan. New York. 1970.

5. Singh R, Nain S. A Mini-Review on Hyperlipidemia: Common Clinical Problem. Interv Cardiol J 2018;Vol.4 No.3:11. doi:10.21767/2471-8157.100081

6. DuBroff R, de Lorgeril M. Cholesterol confusion and statin controversy. World J Cardiol. 2015 Jul 26;7(7):404-9. doi: 10.4330/wjc.v7.i7.404. PMID: 26225201; PMCID: PMC4513492.

7. Shattat GF. A review article on hyperlipidemia: types, treatments and new drug targets. Biomedical and pharmacology journal. 2015 May 3;7(1):399-409. Doi: https://dx.doi.org/10.13005/bpj/504

8. Ginghina C, Bejan I, Ceck CD. Modern risk stratification in coronary heart disease. J Med Life. 2011 Nov 14;4(4):377-86. Epub 2011 Nov 24. PMID: 22514570; PMCID: PMC3227156.

9. Jørgensen T, Capewell S, Prescott E, Allender S, Sans S, Zdrojewski T, De Bacquer D, de Sutter J, Franco OH, Løgstrup S, Volpe M, Malyutina S, Marques-Vidal P, Reiner Z, Tell GS, Verschuren WM, Vanuzzo D; PEP section of EACPR. Population-level changes to promote cardiovascular health. Eur J Prev Cardiol. 2013 Jun;20(3):409-21. doi: 10.1177/2047487312441726. Epub 2012 Apr 18. PMID: 22514213.

10. Inkeles S, Eisenberg D. Hyperlipidemia and coronary atherosclerosis: a review. Medicine (Baltimore). 1981 Mar;60(2):110-23. doi: 10.1097/00005792-198103000-00004. PMID: 7012540.

11.Sharma A, Khanijau MR, Agarwal MR. Hyperlipidemia: A Review Article. Doi: http://ssr-net.com/issues/Vol_5_No_2_December_2019/2.pdf

12. Sundaram M, Yao Z. Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion. Nutr Metab (Lond). 2010 Apr 27;7:35. doi: 10.1186/1743-7075-7-35. PMID: 20423497; PMCID: PMC2873297.

13. Ridker PM, Genest J, Boekholdt SM, Libby P, Gotto AM, Nordestgaard BG, Mora S, MacFadyen JG, Glynn RJ, Kastelein JJ; JUPITER Trial Study Group. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. Lancet. 2010 Jul 31;376(9738):333-9. doi: 10.1016/S0140-6736(10)60713-1. Epub 2010 Jul 23. PMID: 20655105.

14. Tripathi KD. Essentials of Medical Pharmacology. 5 [sup] th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd. 2008:778-9.

15. Joseph, D. Pharmacotherapy, A pathophysiological approach, 8thedn, The McGraw Hill companies, Inc. 2011; pp370.

16. Wouters K, Shiri-Sverdlov R, van Gorp PJ, van Bilsen M, Hofker MH. Understanding hyperlipidemia and atherosclerosis: lessons from genetically modified apoe and ldlr mice. Clin Chem Lab Med. 2005;43(5):470-9. doi: 10.1515/CCLM.2005.085. PMID: 15899668.

17. Gao W, He HW, Wang ZM, Zhao H, Lian XQ, Wang YS, Zhu J, Yan JJ, Zhang DG, Yang ZJ, Wang LS. Plasma levels of lipometabolism-related miR-122 and miR-370 are increased in patients with hyperlipidemia and associated with coronary artery disease. Lipids Health Dis. 2012 May 15;11:55. doi: 10.1186/1476-511X-11-55. PMID: 22587332; PMCID: PMC3439335.

18. Gao W, He HW, Wang ZM, Zhao H, Lian XQ, Wang YS, Zhu J, Yan JJ, Zhang DG, Yang ZJ, Wang LS. Plasma levels of lipometabolism-related miR-122 and miR-370 are increased in patients with hyperlipidemia and associated with coronary artery disease. Lipids Health Dis. 2012 May 15;11:55. doi: 10.1186/1476-511X-11-55. PMID: 22587332; PMCID: PMC3439335.

19. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol. 2009 May;8(5):453-63. doi: 10.1016/S1474-4422(09)70058-4. PMID: 19375663.

20. Simons M, Keller P, Dichgans J, Schulz JB. Cholesterol and Alzheimer's disease: is there a link? Neurology. 2001 Sep 25;57(6):1089-93. doi: 10.1212/wnl.57.6.1089. PMID: 11571339.

21. Gupta R, Mohan I, Narula J. Trends in Coronary Heart Disease Epidemiology in India. Ann Glob Health. 2016 Mar-Apr;82(2):307-15. doi: 10.1016/j.aogh.2016.04.002. PMID: 27372534.

22. Keane WF, St Peter JV, Kasiske BL. Is the aggressive management of hyperlipidemia in nephrotic syndrome mandatory? Kidney Int Suppl. 1992 Oct;38:S134-41. PMID: 1405364.

23. Travis AJ, Kopf GS. The role of cholesterol efflux in regulating the fertilization potential of mammalian spermatozoa. J Clin Invest. 2002 Sep;110(6):731-6. doi: 10.1172/JCI16392. PMID: 12235100; PMCID: PMC151136.

24. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. Prim Care. 2013 Mar;40(1):195-211. doi: 10.1016/j.pop.2012.11.003. Epub 2012 Dec 4. PMID: 23402469; PMCID: PMC3572442.

25.Pettersson C. Studies on the atherogenicity of apoB-containing lipoproteins in type 2 diabetes. Institute of Medicine. Department of Molecular and Clinical Medicine; 2009 Jan 15.

26. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. Natl Vital Stat Rep. 2013 May 8;61(4):1-117. PMID: 24979972.

27. Matthews TJ, Hamilton BE. First births to older women continue to rise. NCHS Data Brief. 2014 May;(152):1-8. PMID: 24813228.

28.Lipid Research Clinics Coronary Primary Prevention Trial. The lipid research clinics coronary primary prevention trial results. American Medical Association; 1984.

29. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA. 1988 Aug 5;260(5):641-51. PMID: 3164788.

30. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy, part V: the discovery of the statins and the end of the controversy. J Lipid Res. 2006 Jul;47(7):1339-51. doi: 10.1194/jlr.R600009-JLR200. Epub 2006 Apr 3. PMID: 16585781.

31. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy: part II: the early evidence linking hypercholesterolemia to coronary disease in humans. J Lipid Res. 2005 Feb;46(2):179-90. doi: 10.1194/jlr.R400012-JLR200. Epub 2004 Nov 16. PMID: 15547293.

32. Steinberg D. Thematic review series: the pathogenesis of atherosclerosis: an interpretive history of the cholesterol controversy, part III: mechanistically defining the role of hyperlipidemia. J Lipid Res. 2005 Oct;46(10):2037-51. doi: 10.1194/jlr.R500010-JLR200. Epub 2005 Jul 1. PMID: 15995167.

33. Steinberg D. The pathogenesis of atherosclerosis. An interpretive history of the cholesterol controversy, part IV: the 1984 coronary primary prevention trial ends it--almost. J Lipid Res. 2006 Jan;47(1):1-14. doi: 10.1194/jlr.R500014-JLR200. Epub 2005 Oct 15. PMID: 16227628.

34. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol. 2009 Jun;6(6):399-409. doi: 10.1038/nrcardio.2009.55. Epub 2009 Apr 28. PMID: 19399028.

35. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation. 1994 Mar;89(3):1333-445. doi: 10.1161/01.cir.89.3.1333. PMID: 8124825.

36. Moynihan R. Surrogates under scrutiny: fallible correlations, fatal consequences. BMJ. 2011 Aug 15;343:d5160. doi: 10.1136/bmj.d5160. PMID: 21844159.

37. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, Genest J, Eisenberg MJ. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009 Oct;122(10):962.e1-8. doi:

10.1016/j.amjmed.2009.03.030. Epub 2009 Aug 19. PMID: 19698935.

38. Jacobson TA, Chin MM, Fromell GJ, Jokubaitis LA, Amorosa LF. Fluvastatin with and without niacin for hypercholesterolemia. Am J Cardiol. 1994 Jul 15;74(2):149-54. doi: 10.1016/0002-9149(94)90088-4. PMID: 8023779.

39.Edeoga HO, Okwu DE, Mbaebie BO. Phytochemical constituents of some Nigerian medicinal plants. African journal of biotechnology. 2005 Aug 19;4(7):685-8. Doi: https://academicjournals.org/journal/AJB/article-full-text-pdf/7C84C0B10671

40. Cunningham AB. An investigation of the herbal medicine trade in Natal/KwaZulu. Institute of Natural Resources, University of Natal; 1988.

41. Belay B, Belamarich PF, Tom-Revzon C. The use of statins in pediatrics: knowledge base, limitations, and future directions. Pediatrics. 2007 Feb;119(2):370-80. doi: 10.1542/peds.2006-0787. PMID: 17272627.

42. Eiland LS, Luttrell PK. Use of statins for dyslipidemia in the pediatric population. J Pediatr Pharmacol Ther. 2010 Jul;15(3):160-72. PMID: 22477808; PMCID: PMC3018249.

43. Bersot TP. Drug therapy for hypercholesterolemia and dyslipidemia. Goodman and Gilman's, The Pharmacological Basis of Therapeutics. McGraw-Hill. 2011:877-908.

44. Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Annu Rev Biochem. 2003;72:137-74. doi: 10.1146/annurev.biochem.72.121801.161712. Epub 2003 Jan 16. PMID: 12543708.

45. Safeer RS, Lacivita CL. Choosing drug therapy for patients with hyperlipidemia. Am Fam Physician. 2000 Jun 1;61(11):3371-82. PMID: 10865931.

46. Pattis P, Wiedermann CJ. Ezetimibe-associated immune thrombocytopenia. Ann Pharmacother. 2008 Mar;42(3):430-3. doi: 10.1345/aph.1K614. Epub 2008 Feb 5. PMID: 18252832.

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