



A REVIEW ON HYPERLIPIDEMIC ACTIVITY

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Abstract: Hyperlipidemia is the most common modifiable cause of atherosclerotic cardiovascular disease. Our understanding of managing hyperlipidemia has led us to the concept of the inverse correlation of low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein (non-HDL) cholesterol with the advent of a major adverse cardiovascular event. This review will provide an overview of lipids and their metabolism. Additionally, it will focus on hyperlipidemia and approaches to its management.

Keywords: Lipid metabolism, Statin-induced myopathy, Bempedoic acid, Niacin, Low density lipoprotein-cholesterol.

INTRODUCTION

lipid metabolism begins with the hydrolysis of a vast percentage (approximately 50-80%) of main TGs in the presence of lipoprotein lipase. Lipoprotein lipase is found at the endothelial site of several peripheral tissues. On the contrary, TGs are present in the residue particles like cholesteryl esters and most lipid-soluble vitamins. Insulin found in the adipose tissue activates the lipoprotein lipase.¹ The enzymic insulin activity is hence amplified after a person consumes a meal rich in carbohydrates and fats. The alignment of these fragments is also changed since CM atoms obtain cholesteryl esters. The modification occurs due to the transfer of cholesteryl esters from cholesterol-rich lipoproteins, a procedure facilitated by the cholesteryl ester transfer protein (CETP). Formerly obtained apolipoprotein E (apo E) enables the liver and other tissues to uptake hepatocytes (the residues).² After the liver's uptake, there is repackaging or metabolization of lipid components of the remnants into VLDLs. VLDLs experience an intravascular metabolism impartially analogous to that of CMs. CM intravascular metabolism pertains to acquiring transferrable apoproteins, CETP-facilitated acquisition of cholesteryl esters, hydrolysis of a considerable portion of TGs, and forming residue particles known as IDLs. Hyperlipoproteinemia and is considered as a key risk factor for cardio vascular disorders (CVD)¹. The causes of hyperlipidemia are mainly life style changes (poor diet, smoking, alcohol). The hyperlipidemia may be primary

ie. Genetic (monogenic, polygenic) or secondary which is associated with diabetes, myxedema, nephrotic syndrome, chronic alcoholism, drugs etc². At least 3/4th of India's population has abnormal levels of cholesterol that increases the risk of cardio vascular diseases according to a study commissioned by the Indian Council of Medical Research (ICMR). Studies have shown that Indians are affected by heart diseases at a much younger age when compared to the people in the West. According to the statistics provided by the Tamilnadu government, 1/4th of all deaths among people in the 25-69 years age groups is due to cardio vascular diseases. There have been data on risk factors such as obesity, diabetes, hypertension and lifestyle habits such as poor diet, smoking and alcohol.. One in ten persons (13%) had high cholesterol level and more than one in five (29.5%) had high levels of triglycerides.³ To make it worse, 72.3% had low levels of HDL (good cholesterol), 11.8% had high levels of LDL (bad cholesterol). HDL or good cholesterol is universally low across the country. The study group found hypercholesteremia in 18.3% of Tamilnadu population⁴. The common treatment for hyperlipidemia is prescription of statins, bile acid sequestrants, fibric acid derivatives and nicotinic acid. Adverse effects associated with these drugs are headache, nausea, bowel upset, rashes, sleep disturbance, abnormal liver function, myositis, hyperuricemia, rise in serum transaminase, muscle tenderness and rise in Creatine Phosphokinase levels.

Table no 1. Hyperlipidemia and cholesterol and triglyceride

Isolated cholesterol elevation	Cholesterol and triglyceride elevation	Isolated triglyceride elevation
Genetic familial hypercholesterolemia	Combined familial hyperlipidemia	Lipoprotein lipase deficiency
Familial defective apolipoprotein B100	Familial dysbetalipoproteinemia (type III)	ApoC-II deficiency (deficiency of lipoprotein lipase activation)
Elevated plasma lipoproteins	Hepatic lipase deficiency	Familial hypertriglyceridemia
Polygenic hypercholesterolemia	Coronary heart disease	Coronary heart disease
Cerebrotendinous xanthomatosis	Cerebral cholesterosis	Cerebral cholesterosis
Sitosterolemia	Beta-sitosterolemia plant sterol storage disease	Phytosterolemia

Table no. 2 Secondary hyperlipidemia causes

Secondary cause	Causative agents/components
Drugs	Diuretics (thiazide), glucocorticoids, sex hormones, beta-blockers, antipsychotics, antiretrovirals, immunosuppressants, retinoic acid derivatives
Diet	Saturated and trans fat, high-sugar beverages and foods, whole milk, red meat, alcohol, excess calories
Diseases	Type 2 diabetes, metabolic syndrome, obesity, hypothyroidism, HIV, PCOS, renal disease (nephrotic syndrome)

Traditional treatment

Indigenous systems of medicine like Siddha, Ayurveda and Unani mainly use medicinal plants for treatment of various ailments of human beings and animals. With the development of these systems, herbal plants are being sought after, both by clinicians and patients in search for new cure of diseases. Herbal medicine is a form of complementary and alternative medicine and is becoming increasingly popular in both developing and developed countries⁴. WHO has described traditional medicine as one of the surest means to achieve total health care coverage of the world's population. In pursuance of its goal of providing accessible and culturally acceptable health care for the global population, WHO has encouraged the rational use of traditional plant based medicines by member states and has developed technical guidelines for the assessment of herbal medicines. Herbal drugs have been used throughout the world and have raised greater attention in recent times because of their diverse nature of curing diseases, safety and high levels of tolerance compared to the conventional medicines. Moreover the herbs with natural combinations of constituents as a whole, are naturally occurring remedies which have proved to be more effective and safer than conventional medicines. Herbs that are used as anti hyperlipidemic agents are *Azima tetracantha*, *Cinnamomum tamala*, *Commiphora mukul*, *Curcuma longa*, *Gymnema sylvestre*, *Moringa olifera*, *Prunus persica*, *Sapindus emarginatus*, *Solanum melongena*, *Terminalia arjuna*, *Terminalia palida*, *Terminalia paniculata*. *Solanum virginianum* Linn., (commonly known as *Solanum xanthocarpum*) belonging to the Solanaceae family, well known as kantangatiri in Tamil, is an annual herbaceous plant mainly growing in India. It is used as a traditional healer of many ailments and has its own importance in Ayurveda to treat fever, cough, asthma, lumbago, piles, urinary diseases, heart diseases and for reducing of fat⁹. It is reported to be non-toxic and safe for human use. All parts of the plant have been found to be noteworthy. The fruits are used as antidiabetic and anthelmintic, the root is used as an expectorant and is useful in asthma, cough and helps to maintain body temperature. The entire plant is used to treat throat infection and other inflammatory problems. The process of drug discovery is very complex and requires interdisciplinary efforts to design effective and commercially feasible drugs. Earlier, drug discovery was a trial and error process. The process of drug development has evolved with time. New understanding of the quantitative relationship between structure and biological activity ushered the beginning of computer-aided drug design. With the help of computers, a new era has begun in drug discovery. The development cost and time is expected to be cut by almost a third by the use of Computer Aided Drug Design. Isolation of active constituents and synthesizing it to target the receptors is a tedious process. The alternative is to make it possible using in-silico studies. There are various softwares like Dock, Auto dock, Argus lab, Glide, Gold, Maestro etc. and various supporting softwares like Chemdraw, Chems sketch, Python, Molgrow etc. available which aid the drug discovery process and make it less tedious. Docking is a search database of molecular structures and retrieves all molecules that can interact with the molecule of interest. It attempts to find the best matching between two molecules. Docking is important to find inhibitors for specific target proteins and to design new drugs. It is acquiring importance as the number of protein structure increases and the efficiency increases accordingly. Some of the successful outcomes of docking studies are the discovery of Amprenavir (Agenerase) for HIV protease inhibition by GSK and Vertex, Nelfinavir

(Viracept) for HIV by Pfizer and Zanamivir (Relenza) for influenza neuraminidase inhibitor by GSK. This study also attempts to evaluate in silico antihyperlipidemic activity, mechanism of action, ADME properties and toxicity profiles for some of the already isolated selected compounds of *Solanum virginianum* Linn., after establishing the antihyperlipidemic activity of *Solanum virginianum* Linn., fruits on rats.¹⁰

HYPERLIPIDEMIA

Dyslipidemia refers to the alteration of one or many of the lipoproteins which may be an elevation of triglycerides or low density lipoprotein cholesterol, or decrease in high-density lipoprotein cholesterol. Elevation of lipid levels alone is termed as Hyperlipidemia.¹¹

Hyperlipidemia- causes

- ✓ Environmental factors¹²
- ✓ Genetic factors
- ✓ Secondary causes
- ✓ Environmental factors¹³
- ✓ Dietary factors and obesity.
- ✓ Genetic factors¹⁴
- ✓ Occur due to single gene or multiple gene defects.¹⁵

Secondary causes¹⁶

- ✓ Diabetes mellitus
- ✓ Hypothyroidism
- ✓ Lipodystrophy
- ✓ Alcoholism

Use of anti-hypertensive drugs, diuretics, Glucocorticoid, Protease inhibitor

- ✓ Obstructive liver disease
- ✓ Nephritic syndrome
- ✓ Acute intermittent porphyria
- ✓ Pathophysiology of hyperlipidemia
- ✓ Exogenous pathway of lipids¹⁷

Fat-soluble vitamins, dietary cholesterol and fatty acids are absorbed in the proximal part of the small intestine. Inside the intestinal lumen, the diet TG are hydrolysed by lipases and are also emulsified with bile acids to form micelles. In the enterocyte, by the addition of a free fatty acid, the cholesterol esterification occurs which results in the formation of cholesteryl esters. Incorporation of triglycerides with fatty acids containing more than 18 carbons atoms are packed with apo-B48, cholesteryl esters, retinyl esters, phospholipids and cholesterol resulting in the formation of chylomicrons. The newly secreted chylomicrons are called nascent chylomicrons which are absorbed into the intestinal lymph and carried directly through the thoracic duct to the blood stream. They are transported to the peripheral tissues before entering the liver. In heart, skeletal muscle and adipose tissue, these

nascent chylomicrons are attached to the lipoprotein lipase anchored by a protein called phosphatidyl inositol-anchored protein, GPIHBP¹⁹. These reactions occur mainly on the endothelial surface of the capillaries. They are hydrolysed by the lipoprotein lipase and the free fatty acids are released.²⁰ HDL transfers the apo C-II to the chylomicron that acts as a cofactor for lipoprotein lipase. The released free fatty acids are taken up by heart and skeletal muscles which are oxidized to generate energy. They can also be re-esterified and stored as triglyceride.²¹ Some of the free fatty acids released will enter into the hepatocytes by binding with the plasma protein like albumin. Due to hydrolysis of its hydrophobic core the resultant chylomicrons progressively decrease in size. The hydrophilic lipids like cholesterol, phospholipids and the protein moiety apolipoproteins on the particle surface are transferred to HDL. These result in the formation of a chylomicron remnant which is about half the diameter of nascent chylomicron.²² The chylomicron remnants are mainly made up of cholesterol and cholesteryl esters. These remnants are rapidly taken up by the liver from the circulation where apo-E act as a ligand. Endogenous pathway of lipids- hepatic lipids The endogenous transport of cholesterol mainly involves. The liver which secretes apo-B lipoproteins. The peripheral tissues where the triglycerides particles are metabolized.

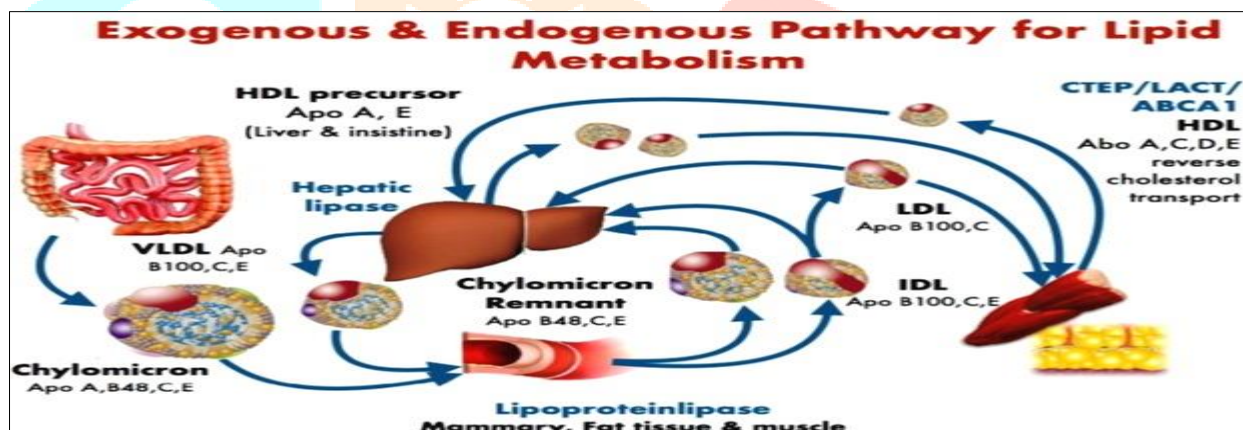


Figure 1: Exogenous and Endogenous pathway of lipids

The VLDL particles resemble chylomicrons in protein composition, where the apo-B48 is replaced by apoB-100. They have the higher ratio of cholesterol and triglycerides. The triglycerides present in the very low density lipoprotein are derived mainly from the esterification of long-chain fatty acids in the liver.²³ The process of combining the hepatic triglycerides with the other major components of the nascent VLDL particle like apoB-100, phospholipids and cholesteryl esters are acquired by the action of the enzyme protein called microsomal triglyceride transfer protein (MTP). In the plasma, HDL transfers the apo-E and the C series of apolipoproteins to the VLDL particle. In the heart, skeletal muscle and adipose tissue, the triglycerides of the VLDL particle are hydrolysed by the lipoprotein lipase enzyme, a process similar to the one occurring to the chylomicron.²⁴ This results in the formation of VLDL remnants which are called as IDL (intermediate density lipoprotein). In the plasma, HDL transfers the apo-E and the C series of apolipoproteins to the VLDL particle. In the heart, skeletal muscle and adipose tissue, the triglycerides of the VLDL particle are hydrolysed by the lipoprotein lipase enzyme, a process similar to the one occurring to the chylomicron.²⁴ This results in the formation of VLDL

remnants which are called as IDL (intermediate density lipoprotein). IDL contains almost same amounts of triglyceride and cholesterol. 40-60% of IDL particle are removed by the liver through endocytosis by binding to apo-E and apoB-100. The remaining IDL is remodeled by hepatic lipase enzyme to form LDL. In this process most of the triglycerides are hydrolysed and result in the formation of LDL which carries apoB-100. In most of the individuals, the concentration of plasma cholesterol is equivalent to the amount of cholesterol present in the LDL particle. In the liver, about 70% of circulating LDL cholesterol is cleared by LDL receptor-mediated endocytosis.²⁵

Type of Cholesterol Values

- ✓ **LDL Cholesterol**
- ✓ <100 mg/dL Optimal
- ✓ 100-129 mg/dL Near/above optimal
- ✓ 130-159 mg/dL Borderline high
- ✓ 160-189 mg/dL High
- ✓ >190 mg/dL Very high

Total Cholesterol

- ✓ <200 mg/dL Desirable
- ✓ 200-239 mg/dL Borderline high
- ✓ > 240 mg/dL High

HDL Cholesterol

- ✓ < 40 mg/dL Low
- ✓ 40-60 mg/dL Normal
- ✓ >60 mg/dL High

Triglycerides

- ✓ <150 mg/dL Normal
- ✓ 150-199 mg/dL Borderline high
- ✓ 200-499 mg/dL High
- ✓ >500 mg/dL Very high

Table 2: Drugs commonly used in the treatment of hyperlipidemia²⁶

Drug (daily dose) Mechanism of action Effect on lipids (%)

HMG-CoA reductase inhibitors

- ✓ Lovastatin (10-80 mg)
- ✓ Simvastatin (5-40 mg)
- ✓ Atorvastatin (10-80 mg)
- ✓ Rosuvastatin (5-20 mg) Cholesterol synthesis by inhibition of rate limiting

HMG-CoA reductase. LDL 20-55

- ✓ HDL 15-30
- ✓ TG 10-35
- ✓ Bile acid sequestrants
- ✓ Cholestyramine (4-16 g)
- ✓ Colestipol (5-30 g)
- ✓ Bile acid absorption,

Hepatic conversion of CH to bile acids, LDL receptors on hepatocytes. LDL 15-30

- ✓ TG not affected
- ✓ Fibrin acid derivatives
- ✓ Gemfibrozil (1200 mg)
- ✓ Bezafibrate (600 mg)
- ✓ Fenofibrate (200 mg) Activity of lipoprotein
- lipase, release of fatty acids from adipose tissue LDL 20-55
- ✓ May LDL when TG is high
- ✓ HDL 15-30
- ✓ TG 10-35
- ✓ Nicotinic acid (2-6 g)
- ✓ Production of VLDL,

Lipolysis in adipocytes. LDL 15-25

- ✓ HDL 20-35
- ✓ TG 20-50

COMPUTER AIDED DRUG DESIGN

Computer aided drug design uses computational chemistry to discover, enhance or study drugs and related biologically active molecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so, how strong the binding would be. Molecular mechanics or molecular dynamics are most often used to predict the conformation of the small molecule and to model conformational changes in the biological target that may occur when the small molecule binds to it. This provides semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring function may be used to provide binding affinity estimates.³These methods use linear regression, machine learning, neural nets or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.

Rational drug design

Rational drug design is the strategy of creating new molecules with a certain functionality, based upon the ability to predict how the structure of the molecule will affect its behavior through physical models.³² This can be done either from scratch or by making calculated variations on a known structure and is usually contrasted with direct evolution. Rational drug designing is a method of finding new medications, based on the biological receptors and target molecules. The objective of drug design is to find a chemical compound that can fit to a specific cavity on a protein target both geometrically and chemically.

Types of drug design

1. Ligand based drug design
2. Structure based drug design
3. Docking

1. Ligand based drug design

It is an indirect approach which relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target. In other words, a model of the biological target may be built based on the knowledge of what binds to it and this model in turn may be used to design new molecular entities that interact with the target.

2. Structure based drug design

Structure based drug design is a direct approach which relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography and NMR spectroscopy. If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics. This combined with the intuition of a medicinal chemist helps in the suggestion of new drug candidates.

3. Docking

Docking simply refers to the ability to position a ligand in the active or a designated site of a protein and calculates the specific binding affinities. Ligand- protein docking has evolved so remarkably during the past decade that docking single or multiple small molecules to a receptor site is now routinely used to identify ligands. Optimal docking procedures need to be fast, generate reliable ligand geometries, rank the ligand conformation correctly (scoring) and thereby estimate the binding energy. A number of studies have shown that docking algorithms are capable of finding ligands and binding conformations at a receptor site close to experimentally determined structures. These algorithms are equally applicable to the

identification of multiple proteins to which a small molecule can bind. The application of this approach may facilitate the prediction of either unknown or secondary therapeutic target proteins are side effects and toxicity of particular drugs. In computational structure-based drug design, the evaluations of scoring functions are the cornerstones to the success of design and discovery.³⁷ Many approaches have been explored to improve their reliability and accuracy, leading to development of three families of scoring functions. These are force-field-based, knowledge-based and empirical-based.

Scoring function

Scoring functions are normally parameterized (or trained) against a data set consisting of experimentally determined binding affinities between molecular species similar to the species that one wishes to predict.

Types

1. Force field based

Force-field affinities are estimated by summing the strength of intermolecular Van der Waals and electrostatic interactions between all atoms of the two molecules in the complex.

2. Empirical

It is based on counting the number of various types of interactions between the binding partners. Counting may be based on the number of ligand and receptor atoms in contact with each other or by calculating the change in solvent accessible surface area complex compared to the uncomplexed ligand and protein.³⁹ These interaction terms of the function may include hydrophobic-hydrophobic contacts, hydrophobic-hydrophilic contacts, number of hydrogen bonds, number of rotatable bonds immobilized in complex formation.

3. Knowledge-based

This is based on statistical observations of intermolecular close contacts in large 3D databases which are used to derive "potentials of mean force". This method is founded on the assumption that close intermolecular interactions between certain types of atoms or functional groups that occur more frequently than one would expect by a random distribution are likely to be energetically favourable and therefore contribute favourably to binding affinity.

Absorption, Distribution, Metabolism and Excretion (ADME) analysis

For a drug to be pharmacologically active and exert its action, it should possess favourable pharmacokinetic properties like Absorption, Distribution, Metabolism and Excretion. In the field of drug research and development many promising drugs face failures because they fail to satisfy the ADME parameters. To rule out the possibility of this, many in vitro studies are frequently used to evaluate ADME properties. Some computational methods (in silico tools) have been evolved to select the most suitable drug molecules.

In silico modeling serves main functions in predicting ADME properties i.e,

A deep rooted knowledge in understanding the relationship of ADME parameters and the underlying (drug likeness property) molecular structural features to which it depends on.

It enhances the interest to the area of posology where it gives information about the drug dosage and frequency. This in turn reflects issues on bioavailability, crossing various biological membranes like brain, ocular and dermal penetration. These are the essential factors and criteria to look in, for a drug to be pharmacologically active and evolve as a successful clinical candidate in the pharmaceutical research.

Prediction of ADME related parameters

Absorption

To investigate this property in silico model uses simple parameters like log D (diffusion coefficient) and polar surface area which are the descriptors for hydrogen bonding capacity and log P (partition coefficient) values. These values should fall under the prescribed values as per the rule of thumb which determines the extent of absorption.

Bioavailability

Factors like size and shape of molecule, lipophilicity and flexibility determines the bioavailability.

Blood Brain Barrier penetration

In order for a drug to cross the blood brain barrier (molecule targeted to brain), as per the rule of thumb, the molecule should have log P values closer to 2 with a molecular mass of <450 Da and/ or with a polar surface area (PSA) <100 Å.

Dermal and Ocular Penetration

For dermal and ocular route it should satisfy the existing parameters like log P (partition coefficient) for aqueous solubility, molecular weight and molecular flexibility.

Metabolism

Various in silico approaches exist in evaluating the metabolism namely QSAR and 3D QSAR. Apart from those, computational chemists have updated the structural details in the data bases and tools for predicting metabolism. It also reveals the toxicity related to the molecular fragments formed by metabolic process.

Evaluation of in silico toxicity

Toxicity is one of the major criteria to be considered for a molecule to shine as a successful clinical candidate in the pharmaceutical research. About 20-40% of the promising drug candidates fail because of high toxicity. Commercial in silico tools estimate toxicity and provide information by the use of QSAR (parameters and descriptors) or scientific literature.⁴⁷

In silico approaches like OSIRIS property explorer, predict carcinogenicity, mutagenicity, teratogenicity, immune toxicology, irritation, sensitization etc.

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