“Recent Advances in the Understanding and Management of Hyperlipidemia: A Comprehensive Review”

Richa Chandra[1], Pratima Katiyar[1], Kalpana Kushwaha[1*]

[1]School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, U.P, India

[2]Faculty of School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, U.P, India

[3]Faculty of School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, U.P, India

Correspondance: Dr. Kalpana Kushwaha, PhD, Faculty of School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, U.P, India
Email: kalpanakushwaha@csjmu.ac.in

ABSTRACT

Hyperlipidemia has historically been an abnormal condition in which plasm lipoproteins carrying triglycerides, cholesterol, and phospholipids increase to their normal range. This elevation in lipoproteins leads to the risk of cardiovascular diseases including stroke cardiac arrest, atherosclerosis, and other metabolic disorders. It lowers levels of High-Density Lipoprotein while raising Low-Density Lipoprotein levels. There are two forms of hyperlipidemia, Primary and Secondary. The main contributory factor of Primary hyperlipidemia is a genetic disorder called familial, and Secondary hyperlipidemia is due to health conditions like hypothyroidism, obesity, diabetes, long-term alcohol use, and beta-blockers medication use. This medical condition can be managed by a change in lifestyle in combination with pharmacotherapy to control lipid levels. Additionally, with conventional treatment, drug delivery technique innovation has a major influence on hyperlipidemia treatment. This review article focuses on this disease and various forms of hypolipidemic drugs and also covers topics including symptoms, pathophysiology, risk factors, and management. Treatment and prevention strategies include diagnosis, prescribed medication, increased physical activity, eating a healthy diet, monitoring, medical therapy, and reassessing. There has been discussion of recent advancements in new research on diagnosing and managing this disorder. Future directions, for novel drug technology are discussed as well to provide more ideas for improving the safety and treatment of patients.

KEYWORDS- Hyperlipidemia, Risk Factors, Diagnosis, Lifestyle, Strategies, Advancement

INTRODUCTION

Traditionally, hyperlipidemia has been defined as an unusual condition in which lipoproteins that carry cholesterol or triglycerides exceed a random normal limit [1]. It significantly affects atherosclerosis and is recognized as a primary risk factor for coronary diseases [2]. A metabolic disorder known as hyperlipidemia affects the serum lipid and lipoprotein profile due to a quantitative rise in the net levels of total cholesterol (TC), triglycerides (TAG), very low-density lipoproteins (VLDL-C), and low-density lipoprotein cholesterol (LDL-C), and a corresponding decrease in the blood circulation's concentrations of high-density lipoproteins [3].

This is an intricate set of disorders classified as primary or secondary based on etiology.

i) Primary hyperlipidemia (Familial hyperlipidemia):

This, commonly referred to as familial hyperlipidemia, is believed to be caused by genetic abnormalities. It can be classified as polygenic, stating the condition arises from several gene defects, or monogenic, suffering from a single gene defect. Distinguishing primary hyperlipidemia can be achieved via searching into specific abnormal lipoprotein patterns, which can be summed up as listed below:

 Type I: Abnormal triglyceride levels and high cholesterol.

 Type II: Balanced triglycerides with hypercholesterolemia

 Type III: Increased triglycerides and cholesterol levels.

 Type IV: Excessive uric acid, atheroma, and fats.

 Type V: Triglycerides that are higher than normal.

ii) Secondary (Acquired hyperlipidemia):

It can occur as a result of other medical disorders such as diabetes, glomerular syndrome, persistent alcoholism, hypothyroidism, and the use of drugs such as beta-blockers, corticosteroids, and oral contraceptives. When there is significant hypertriglyceridemia and subsequent hyperlipidemia, pancreatitis may develop. If there is notable hypertriglyceridemia and secondary hyperlipidemia, pancreatitis can develop [4].

Causes of HL

A lifestyle that is high in fat (more than 40% of caloric intake), elevated levels of saturated fats (10% of caloric intake), increased cholesterol (more than 300 mg/day), or treatable medical conditions are the main causes of hyperlipidemia (HL). Abnormal levels of cholesterol are because of a diet high in fat, excessive alcohol consumption, being overweight, inadequate physical activity, and smoking, along with other unhealthy habits. Additional contributory factors include pregnancy, diabetes, polycystic ovarian syndrome, renal disease, and underactive thyroid gland [5]. Additional causes that hyperlipidemia occurs

• Obesity.

• Genetic or inheritance.

• Smoking.

• Beta-blockers, estrogen, and corticosteroids are among the medicines that can increase the risk of hypertriglyceridemia.

• Kidney failure, hypothyroidism, alcohol, steroids, etc.

• Little or no physical activity [6]

Symptoms of Hyperlipidemia

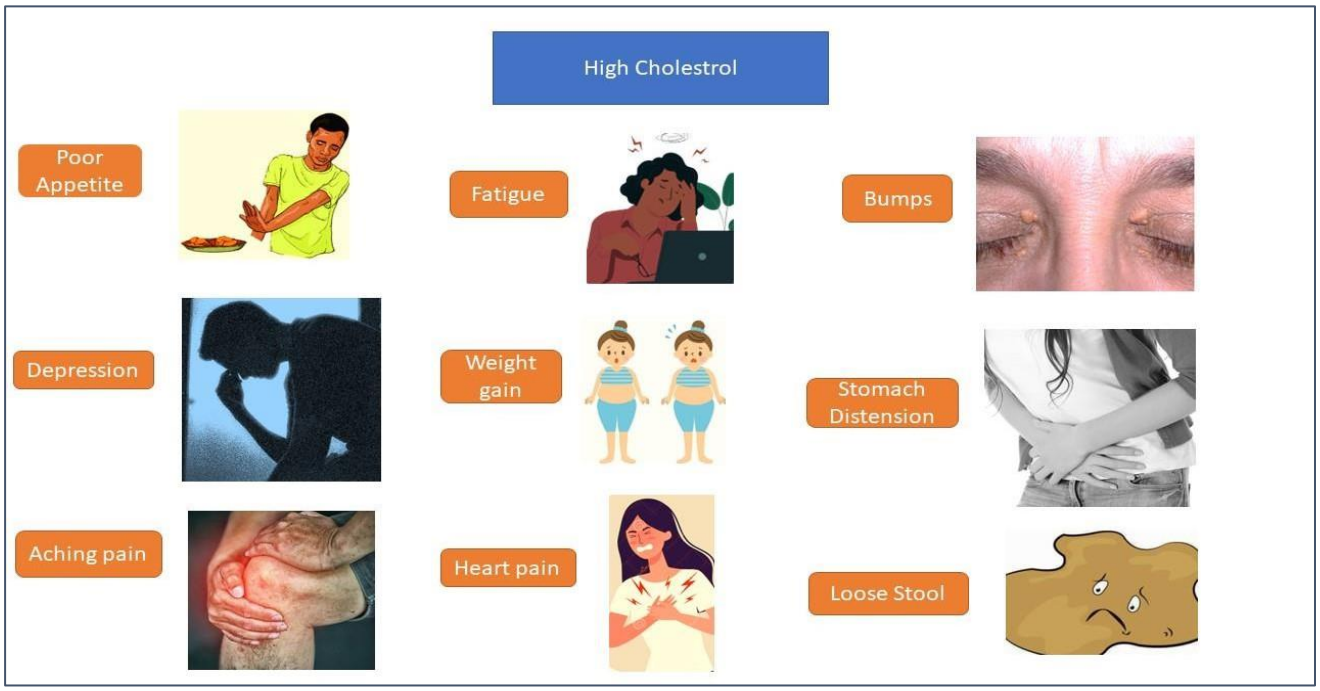

Figure 1: Symptoms of hyperlipidemia

Routine blood tests help individuals recognize they have hyperlipidemia, even though the condition might not show obvious signs or symptoms. Patients may generally experience chest pain, athermanous plaques in blood vessels, abdominal pain, spleen hypertrophy, hepatic enlargement, cardiac issues, and stomach pain [7].

PATHOPHYSIOLOGY

High cholesterol levels can cause plaque to accumulate and form in the vessel walls, which may result in atherosclerotic cardiovascular disease [8]. Three different phases are commonly used to categorize the pathophysiology of atherosclerosis: the early stages, its progression, and its consequences. LDL or bad cholesterol has an extensive effect during the initial stage [9].

Based on existing research and reviews, endothelial damage to blood vessels is the cause of hyperlipidemia. This damage leads to nitric oxide loss at the region of injury, increased inflammatory activity around the afflicted location, and lipid accumulation in the lowest layer of the endothelium wall, where macrophage cells engulf the lipids and produce what is known as a foam cell containing cholesterol [10]. Necrosis, apoptosis, and mitochondrial dysfunction will occur from forming foam cells. Smooth muscle cells encircling the foam cell concurrently, prevent the foam cells from deteriorating and resulting in fibrotic plaque. In addition, Plaque rupture and thrombosis are spurred through tissue factors that activate platelet activity. Plaque can form gradually, causing stenosis in blood vessels, or rapidly, occluding blood vessels. Lipid plaque continues to be the main factor in the occurrence of CVD and the declining state of patient health in both scenarios. Patients suffering hyperlipidemia can additionally have dysfunction of the tendon, specifically the patellar tendon, in addition to cardiovascular disease (CVD). This is because, over time, hyperlipidemia releases an increased quantity of macrophages. Over time, hyperlipidemia causes tendons to become more inefficient and more susceptible to damage because it increases the amount of macrophages in the tendon tissues, which break down the collagen fibers and replace them with lipids [11].

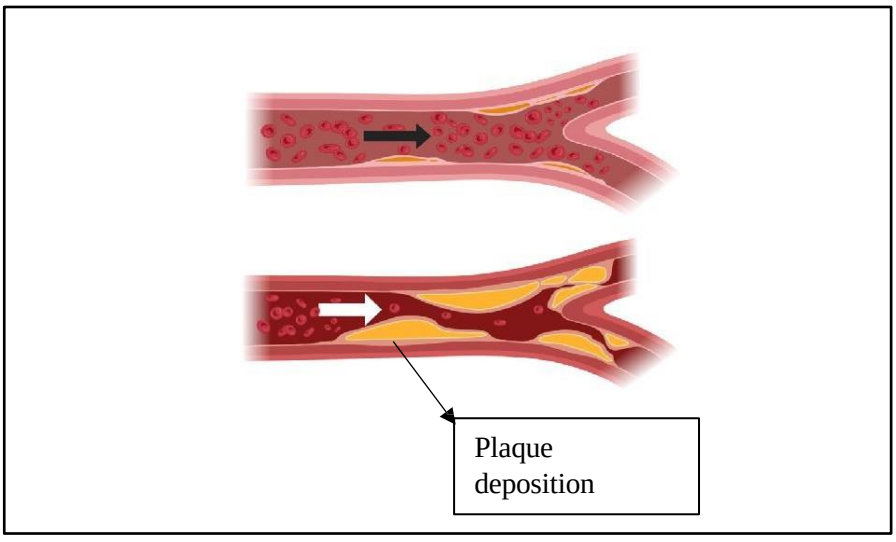

Figure 2: Plaque buildup in the vessel walls can result in cardiovascular diseases.

Lipid abnormalities: Lipid levels can rise or fall which causes several kinds of health problems affecting the body that are referred to as diseases. These medical conditions, usually result in increased triglyceride, low-density lipoprotein (LDL), or lipid levels. HDL, a good fatty acid, is required for the body because it helps the body eliminate bad cholesterol. In the same way, triglycerides and other undesirable fats like fatty LDLs build up and cause damage to the arteries, which has a major impact on cardiovascular health. When compared to a lower level of lipids, a higher amount of fat buildup in the body, known as hyperlipidemia, causes more health problems (Natesan and Kim, 2021). The term "hyperlipidemia" describes a class

of severe lipid diseases brought on by an unusually high blood level of undesirable fats (Verma, 2017). It categorized hyperlipidemia according to the type of lipid. Moreover, the body's excessive accumulation of fat leads to several diseases. Diabetes and cardiovascular diseases, both of which were asymptomatic at the time, are among the most harmful outcomes. These health problems are currently the most prevalent in the digital world.

Role of Lipoproteins in Cholesterol Transport and Metabolism: Major lipoprotein variants that are important for the bloodstream's transportation and metabolism of cholesterol and other lipids:

1. Chylomicrons
2. VLDL (Very-Low-Density Lipoproteins)
3. LDL (Low-Density Lipoproteins)
4. HDL (High-Density Lipoproteins)

RISK FACTORS

Numerous risk parameters, such as age, gender, and genetic predisposition to the disease, are linked to cardiovascular disorders. A positive family history of cardiovascular disease (CVD) or instances of early CVD manifestation in the family are examples of major risk factors. There are several risk factors for atherosclerotic cardiovascular disease (ASCVD), and these can be further divided into modifiable and non-modifiable. Additional problems that are classified as nontraditional risk factors and are linked to the development of early atherosclerosis include hypothyroidism, HIV infection, congenital cardiac abnormalities, cardiomyopathy, organ transplantation, chronic renal diseases, and bipolar and depressive disorders in adolescents [14].

a) Primary Hyperlipidemia

Familial Diseases of Lipoproteins: It is possible to develop a familial plasma elevate for, any of these lipoprotein components. Most of the cause is inherited. Familial hypercholesterolemia is the most prominent type of this condition (FH). In the years ahead, research will increasingly use recombinant DNA technology and site-specific mutagenesis to uncover the distinct functions of apolipoproteins in lipoprotein metabolism plus the relationships between function and its related structure [15].

Family History: Based on a natural history study, 50% of men and 25% of women with FH are expected to have had clinical CVD by the time they are 50 years old due to elevated LDL-C levels. A family history of cardiovascular disease is a major risk factor for the condition [16,17]. According to research, between 25 and 55% of children have a family history of early-onset CVD, so individual lipid monitoring is recommended [18,19].

b) Secondary Hyperlipidemia

Physical Inactivity: Inactive activities are related to elevated blood lipid levels, according to recent studies. Furthermore, watching too much television leads to lower HDL-C and higher TG, most likely because it utilizes less energy. Exercising significantly enhances blood pressure, lipid profile, insulin sensitivity, serum glucose levels, and cardiorespiratory fitness [20,21].

Dietary: In most civilizations, the price of foods that are rich in energy is often less than that of foodstuffs lower in energy, like fruits and vegetables [22]. Studies demonstrate that when individuals live in urban areas, their energy consumption doubles. This is mostly because, in comparison to those who live in rural regions, these individuals consume more fruits and vegetables, less whole grain foods and fiber, and more fats of all types [23]. Certain dietary changes may increase the prevalence of obesity and have a major effect on people's overall health and well-being of an individual.

Obesity: The body's excessive fat buildup and uneven distribution, usually coupled with metabolic dysregulation, are the hallmarks of obesity. Apolipoproteins are essential structural components in the development of dyslipidemia, a disorder characterized by abnormal lipid levels that are commonly associated with obesity. Apolipoproteins notably impact energy use, inflammatory responses, and lipid metabolism—all of which lead to the emergence of obesity [24]. Although there is some variation, being overweight correlates with elevated lipid levels and is a substantial risk factor for hyperlipidemia [25]. Following the identification of secondary hyperlipidemia reasons that could worsen atherosclerosis, children should also be examined for dyslipidemia [26].

Age: Lipid metabolic enzymes undergo significant modifications by aging and are regulated through multiple longevity-related processes. Since lipids act as signaling molecules, they also actively regulate lifespan and health span. It was found that people over 75 years of age have increased HDL concentration in a study involving 2128 participants [27].

Lifestyle factors: In addition to age, ethnicity, lower family income, and a lower educational level, poor access to public health care is linked to weight gain and an increased risk of CVDs [28,29]. Poor lifestyle habits include smoking, consuming alcohol, not exercising, getting little to no sleep, and eating poorly [30]. Being stressed at work has also been overlooked as a risk factor for CVDs. Certain government employees, like police officers and firefighters, constantly manage demanding workloads, shift rotations, late-night shifts, and unpredictable work schedules [31,32]. Atherosclerosis and cardiovascular diseases are often led by prolonged exposure to stressful conditions and crises. Research results demonstrated that lifestyle habits (such as drinking alcohol, smoking, and betel nut chewing) were strongly correlated with the risks of hyperlipidemia.

Smoking- Cigarette smoking has been identified as a separate, controllable risk factor for CVDs and atherosclerosis. It should be noted that additional investigation is needed to determine how exposure to environmental tobacco smoke (ETS) and perceived psychosocial work stress interact to cause hyperlipidemia.

Alcohol consumption- A 2017 observational study including 7,641 Europeans aged 50 and older observed low HDL or high triglyceride levels were present in 1,591 (20.8%) of the participants. Additionally, these patients were more likely to have type 2 diabetes mellitus, obesity, and alcohol use beyond the advised weekly limit. Of those with increased TG and low HDL, 55% did not receive lipid therapy [33].

CLINICAL MANIFESTATION

Hyperlipidemia induces the body's production of free radicals to increase rapidly, which in response encourages the emergence of other pathological diseases. Risk factors include coronary heart disease, myocardial infarction, stroke, heart attacks, cerebrovascular disorders, and the emergence of diabetes [34].

The main focus of treatment for individuals with hyperlipidemia is to reduce their risk of developing ischemic heart disease and any subsequent cardiovascular or cerebrovascular disorders [35]. A disorder identified as hyperlipidemia develops when the blood contains excessively high amounts of lipids or fatty substances [36]. The occurrence of atherosclerosis and its accompanying disorders, such as peripheral vascular disease, cerebrovascular disease, cardiovascular disease, and brain strokes, are typically linked to adverse effects [37].

1] Atherosclerosis: is described as an accumulation of calcification, fibrous materials, and lipids within the major arteries. The process of endothelium activation, which includes inflammatory pathway activation and vessel narrowing, triggers the formation of atheroma plaque. All of these mechanisms combine to trigger cardiovascular issues, which remain the world's top cause of fatality [38].

When cholesterol accumulates in the arterial wall, a process known as atherosclerosis occurs, hardening the arteries while making them narrow. Hyperlipidemia causes atherosclerosis and indications associated with it, including peripheral vascular, cerebrovascular, and coronary diseases [39]**.** Generally, a plaque is composed of three parts:

- Atheroma: a yellowish, soft, fatty nodular mass in the middle of a larger plaque that contains immune cells known as macrophages.

- A coating of crystal cholesterol

-The outermost layer which is calcified. One of the primary causes of cardiovascular disorders is atherosclerosis [40].

2] Cardiovascular Diseases

a) Myocardial infarction: A myocardial ischemia is a complete or partial blockage of one or more heart arteries, obstructing blood flow and oxygen. It is often caused by the rupture of an atherosclerotic plaque and is capable of obstructing heart cells, which can result in death [41].

b) Coronary Artery Disease: Atherosclerosis: The primary etiology of CAD, is characterized by the buildup of excess lipids and the emergence of fibrous plaques within the arterial walls. This process causes the arteries that provide blood to the myocardium to constrict, which hinders blood flow and leaves the heart with insufficient oxygen to meet its needs [42].

c) Ischemic stroke or cerebrovascular accident: Stroke is the fourth most common cause of death. Strokes usually happen when an artery in the brain is blocked by a blood clot or a piece of atherosclerotic plaque that breaks off inside a small blood vessel. Several investigations have discovered that a 15% reduction in total cholesterol and low-density lipoprotein levels significantly lowers the risk of having a first-time stroke [43].

d) Peripheral Artery Disease: Complete or partial blockage of one or more of the peripheral noncardiac, non-intracranial arteries in the upper and lower limbs is often referred to as PAD. This obstruction can result in tissue loss or decreased blood flow [44]. Diabetes mellitus (DM) continues to be an important risk indicator for PAD, and the prevalence of PAD in DM patients is over two times that of the general population. Moreover, people suffering from PAD along with DM might result in diabetic foot ulcers (DFUs), which may trigger hyperglycaemic crises, higher hospital admission rates, worse quality of life, and mortality.

e) Angina Pectoris: Angina is a symptom of a more severe cardiac issue rather than a separate health illness. Chest pain, discomfort, or a squeezing feel are its defining characteristics. Angina is mostly caused by a decline in blood flow to part or all of the heart muscle. The condition when the coronary arteries are entirely or partially obstructed is often a sign of coronary heart disease (CHD) due to inadequate blood flow [45].

3] Hyperlipidemia-related Complications

Acute Pancreatitis (AP): is a prominent disorder with several causes. If the condition known as hypertriglyceridemia, which is unusual but can cause AP, becomes too severe, that may turn deadly. AP is triggered by HTG in 1-7% of people with increased triglyceride levels [46]. Increased levels of serum triglycerides are induced by HTG, an increased VLDL, and chylomicron level [47]. AP is attributed to an epiphenomenon called hyperlipidemia.

Cholesterol Gallstones: The latest research indicated a significant link between hyperlipidemia and human gallstones, which links high cholesterol to gallbladder conditions like cholesterolosis and gallstone disease [48]. An alteration in lipid metabolism, a crucial component in the pathogenesis of cholesterol gallstones, is the primary source of the corresponding rise in bile cholesterol levels [49]. The main components of gallstones which consist of cholesterol are triglycerides and cholesterol. The pathophysiology of cholesterol gallstones begins with the overproduction of cholesterol by the liver, resulting in the bile duct

becoming saturated with cholesterol [50]. Gallstones, usually rich in cholesterol, are partially caused by abnormal lipid metabolism. Serum lipid abnormalities would therefore signify a potential for the emergence of cholesterol gallstones.

DIAGNOSIS

As hyperlipidemia normally shows no signs or symptoms, a blood test is needed to diagnose it. The most prevalent screening method to detect hyperlipidemia is a lipid profile [51]. A routine blood test measuring the levels of LDL, HDL, VLDL, and triglycerides is commonly carried out to detect hyperlipidemia [52]. Regular lipid screening is usually recommended to be performed when a male patient reaches the age of 35 (assuming that there are no additional cardiovascular risk factors) or 25 (when there are other cardiovascular risk factors in the patient). Similarly, if a woman has no other known cardiovascular risk factors, she should begin routine lipid screening at age 45. If she has any cardiovascular risk factors, she should begin screening between the ages of 30 and 35 [53].

The fasting lipid profile check is the main laboratory test performed, and it usually includes a few things:

- Total cholesterol, HDL, LDL, and triglycerides.
- A VLDL, total cholesterol: LDL, HDL, and for an even more thorough examination, HDL ratios can be added.
- To prevent altering the lipid panel outcomes (mostly the triglyceride levels), one must avoid eating or drinking anything other than water for 9 to 12 hours [54]

MANAGEMENT

Lifestyle Modification

Dietary Changes:

Overall, a balanced diet should increase fiber intake while decreasing the consumption of cholesterol and saturated fat [55,56]. Limiting consumption of saturated fatty acids—specifically, animal fats—has a significant influence.

For example, among individuals with elevated risk, a Mediterranean diet supplemented with extra almonds or olive oil lessens the related risk by 30% (Estruch *et al*., 2013).

It is interesting to know that eating nuts decreases LDL cholesterol, therefore it is uncertain whether it has an advantageous effect on the lipid profile for at least part of the risk reduction (Wu *et al*., 2014).

Moderate Alcohol Consumption: Triglyceride levels can be decreased by more than 50% with strict restrictions on alcohol intake and a decrease in the amount of fast-absorbing carbohydrates consumed (Hegele *et al*., 2014).

Physical Activity:

Among the multiple, well-known benefits of physical activity are improved cardiovascular, mental, behavioral, and musculoskeletal health. More specifically, exercise enhances blood pressure, lipid profile, insulin sensitivity, serum glucose levels, and cardiorespiratory fitness [60,61]. Furthermore, workouts strengthen bone density and balance, thus helping adults and children prevent falls and injuries [62].

A recent study revealed that increased physical activity minutes were associated with improved lipid concentrations (HDL-C and TG levels) in a dose-response manner. This finding supports the guidance that individuals between the ages of 6 and 17 ought to indulge in at least three days of bone- and muscle-strengthening activities in addition to 60 minutes of moderate-to-intense activity each day [63,64,65].

Both healthy individuals and children having obesity or hyperlipidemia must participate in consistent physical activity to improve BMI, eliminate fat in the body, elevate HDL-C, and decrease TC, TG, and LDL-C.

Smoking: Living a healthy lifestyle and abstaining from tobacco use is advisable for an increased lipid profile. If smoking is a current issue, starting to give up smoking may help normalize the lipid profile [66,67].

Adopt a healthy lifestyle to modify risk factors	*Treatment for risk factors*
Adopt a balanced diet ***Stop using tobacco*** ***Prevent and manage overweight/obesity*** ***Regular exercise***	Appropriate treatment following local guidelines for Diabetes Hyperlipidemia Hypertension Consider aspirin and statins

Table1: Strategies for managing the risk factors and treating cardiovascular disease [68,69]

Pharmacological Management

Statins: Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are the first-line treatment for hyperlipidemia. They specifically assist raise HDL-C levels and lower TG and LDL-C levels in people with severe and familial hypercholesterolemia [70]. The drugs most widely prescribed are pravastatin or rosuvastatin (over the age of 8), while atorvastatin, simvastatin, or lovastatin are advised for those above the age of 10

Cholesterol Absorption Inhibitors:

The primary purpose of ezetimibe, a cholesterol absorption inhibitor, is to lower LDL-C levels in patients with severe or hereditary hypercholesterolemia. Gastrointestinal problems, hepatotoxicity, and myopathy are signs of adverse effects. It hasn't been thoroughly studied as a single-agent therapy yet, but it is frequently used as an adjuvant to other drugs [71].

Ezetimibe combined with a moderate-intensity statin should be considered as an alternative for treating patients with acute coronary syndrome who are intolerant of high-intensity statin therapy [72].

Fibric Acids:

Fibric acids called fenofibrate and gemfibrozil lower TG and LDL-C levels while increasing HDL-C levels to cure hypertriglyceridemia. Perhaps taken in combination with statins.

Nicotinic Acid:

To manage familial or severe hypercholesterolemia niacin, also known as nicotinic acid, elevates HDL-C levels by over 30% and cuts triglycerides by about 25%. The possibility of significant adverse reactions including flushing, glucose intolerance, migraines, hepatotoxicity, and myopathy make it uncommonly used.

Omega-3 Fatty Acids:

In cases of severe hypertriglyceridemia, fish oils, which are long-chain omega-3 fatty acids, are used as an adjuvant by suppressing TG levels. It is not advisable to be used as an individual therapy as it works better on adults than on children [73]

Bile Acid Sequestrants (Resins):

LDL-C levels are reduced by bile acid sequestrants or resins. Commonly, it causes gastrointestinal complications, such as constipation, bloating, and discomfort in the abdomen. Example- cholestyramine [74].

Personalized Treatment

Monitoring and Follow-Up

Guidelines for lipid screening, encompassing a "lipid profile" to estimate cholesterol and triglyceride levels, have been established by multiple expert organizations.

For male patients, not having any additional cardiovascular disease risk factors, lipid screening should be performed at the age of 35; if they do, screening should be done at age 25. If no additional cardiovascular risk factors exist, then periodic lipid screening in females begins at age 45. It starts between the ages of 30 and 35 if the person has extra cardiovascular disease risk factors [75]. More frequent screening is required as a patient's risk of cardiovascular

disease increases, and lipid screening is advised for those who are at lower risk every five years [76].

Liver function tests should be conducted to check out liver dysfunction before using a statin for high LDL levels, as statins could aggravate it. It's vital to always talk about improving one's lifestyle, giving up smoking, and adopting a healthy diet. Before commencing pharmacological therapy, it matters to analyze the positive and negative aspects of each drug.

Talking with the patient about drug side effects and being prepped to point out any potential adverse effects or interactions from the prescription medications that the healthcare provider has given are part of it.

To keep the patient secure and potentially stop the progression of the disease, these professionals, their specialized fields, and the patient should have optimal interaction among them. This will help ensure appropriate medication adherence and treatment.

Patient Education

Information about compliance with medication, undesirable effects, interactions, and the general risks versus positive effects of the prescribed medicine must be given to the patient by their medical professional and pharmacist. The patient should also be informed of the possible consequences of skipping doses and alternative treatment choices.

Consideration of Risk Factors

When assessing lipid-lowering medication, the predicted 10-year risk for ASCVD (Atherosclerotic Cardiovascular Disease) should be determined using the Multi-ethnic Study of Atherosclerosis (MESA) 10-year ASCVD risk calculator, which incorporates the coronary artery calcium (CAC) score [77].

One of the most important objectives of universal screening is to identify participants who have familial hypercholesterolemia (FH). FH affects 1 in 250 people, and if the condition is not detected and treated, patients may develop serious coronary artery disease and other cardiovascular issues during their younger life.

Reverse cascade screening, another method of detecting the impact on the members of the family can be made attainable by universal screening for adolescents [78].

TREATMENT

Studying Lipid-lowering Drug Benefits

Statins: They serve as the first line of treatment for cholesterol level reduction; supplementary lipid-lowering drugs are incorporated to manage severe hypertriglyceridemia, statin intolerance, or to improve statin efficacy. At larger doses, statins can lower LDL and

triglyceride levels while raising HDL levels [79]. However, there have been several kinds of side effects caused by statins, like pain in the muscles, liver damage, and type 2 diabetes [80].

Fibrates: It has been claimed that fibrates may elevate HDL by 5 to 20% while reducing triglycerides by up to 50%. Fibrate negatively impacts clinical results even though it suppresses lipids. They are specifically used to lessen the risk of pancreatitis and lower triglycerides [81].

Nicotinic Acid: HDL-C (high-density lipoprotein cholesterol) is raised considerably by niacin however it is unknown if this increases the clinical results of patients treated with statins. When Niacin is used with statins and ezetimibe, it helps to reduce LDL in those people who suffer from very high cardiovascular risk, for instance, secondary prevention is ineffective for someone with homozygous or heterozygous familial hypercholesterolemia [82].

PCSK9 Inhibitors: A new class of drugs approved for lowering LDL have been identified as PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9). It has been determined that they can reduce LDL by up to 60% in statin users. The FDA has approved the monoclonal antibodies alirocumab and evolocumab for use in adult patients with heterozygous familial hypercholesterolemia or clinical ASCVD who require further LDL-cholesterol decline in addition to dietary modifications and effectively tolerated statin therapy. In addition to conventional LDL-lowering medications such as ezetimibe or statins, the FDA has authorized evolocumab for use in adult patients with homozygous familial hypercholesterolemia who need further LDL-C reduction [83].

Bempedoic Acid: By inhibiting ATP-citrate lyase (ACL) through an extended chain of acyl-CoA synthetase-1 (ACSVL1), it acts as an upstream of HMG-CoA reductase and activates bempedoic acid in the liver. LDL-C clearance is accelerated by the upstream action because it aids in the upregulation of LDL-R. Additionally, bempedoic acid works well for patients who are allergic to statin therapy since it prevents myalgias, one of the most common side effects of statin medications. An oral medication called Nexletor can be used daily without the need for statins and assists in lowering LDL-C [84].

Bile acid sequestrants or BAS: Colestipol, colesevelam, and cholestyramine are examples of BAS (bile acid sequestrants) [85]. Large, positively charged, non-absorbable polymers known as bile acid sequestrants (BAS) are medications used to treat HL. As it binds in the colon, it stops them from being reabsorbed, potentially lowering blood cholesterol levels. They generally produce few side effects and are well tolerated [86,87].

In the intestine, cholestyramine is the resin that bonds itself to bile acids and inhibits them from reabsorbing into the bloodstream. Cholestyramine is available as a granule or powder for oral administration that can be diluted with water or other liquids. Abdominal pain, nausea, bloating, and constipation are frequently experienced adverse effects [88].

A synthetic polymer called colesevelam binds bile acids in the intestine inhibiting the reabsorption into the bloodstream [89].

A Drug	The mechanism	Adverse effects
Statin	To reduce cholesterol	Digestive disturbance, liver
Rosuvastatin, Simvastatin, and Atorvastatin	Suppression of HMG CoA reductase, and synthesis in the liver	Variations in function tests, muscle stiffness, myositis and myalgia
Clofibrate	Reduces the level of TG in the serum	Diarrhea, arthralgias, and feeling of nausea
Gemfibrozil	Minimizes TG in plasma by 40-55%	Nausea, diarrhea, and abdominal discomfort
Nicotinic acid and derivatives	Suppresses lipolysis and the release of free fatty acids	Headache, dizziness, vomiting, dyspepsia, stomach disturbance
bile acid-binding (anion exchange) resins	Bile acid-derived cholesterol is entirely reabsorbed	The drug's texture, unpleasant taste, and constipation
omega-3 fatty acid	Significantly hinder the production of triglycerides	gastrointestinal distress, and extended bleeding duration
Cholestyramine	Causes Chol catabolism by binding bile acid	Indigestion, and nauseous feeling
Neomycin	Decreases plasma Chol by 10%-15%	Diarrhea due to malabsorption

Table 2: This table presents the list of anti-lipidemia drugs and how they help to control fats or cholesterol levels at various body parts through various metabolic pathways. It also emphasizes the negative side effects of the treatments [90,91].

Innovation in Drug Delivery and Emerging Therapies

Nanotechnology

Nanoparticles:

The colloidal particles with a diameter of less than 1 nanometer are called nanoparticles (NPs). The medication is typically encapsulated, trapped, or abstracted within the NPs matrix using polymers that can sustain drug release over time, guaranteeing drug distribution and accumulation in the desired tissues and enhancing therapeutic benefit while reducing systemic adverse effects [92,93].

Liposomes are lipid vesicles that resemble cells and often consist of organized phospholipid bilayers. Non-toxicity, non-immunogenicity, sustained-release medication, extended drug action time, altered drug distribution in vivo, improved drug efficacy, decreased side effects of drugs, and several more are some advantages of liposomes as a drug carrier.

With their amphiphilic traits, polymer-drug conjugates can be taken orally and are composed of an inner drug-incorporated core and an outer dense biocompatible shell [94,95]. The outer layer lowers absorption via the GI tract, extending the time when the medicine is concentrated in the bloodstream and optimizing the control of drug delivery.

Polymers may enhance the delivery of statins and their beneficial effects in CAD patients in several ways, such as better target-specific interaction and increased oral bioavailability [96,97].

Hydrogels:

Three-dimensional networks of hydrophilic polymers, known as hydrogels, are cross-linked chemically or physically and have an affinity to swell, absorb, and retain a huge amount of water [98].

Niacin is frequently used as an anti-hyperlipidemic drug because it can increase HDL and decrease TC and LDL-Cholestrol by suppressing the formation of hepatic triglycerides [99]. The increased intestine targeting efficiency and fewer systemic side effects characterize this efficiently controlled niacin (NA) drug delivery method.

Category	Structure	Drug loading	Advantages	Limitations
Polymeric nanoparticles	Lipophilic core polymer-based nanoparticles, Nanospheres/ Nanocapsules		Very stable and minimal drug leaking	Intravenous toxicity
Liposomes	Lipid layer	Chemical bonding/ physical encapsulation	Excellent compatibility and lack of immunogenicity	Hydrophilic medication with low stability and rapid leaking
Polymeric micelles	Structure generated via self-assembly of the core and shell		It's easy to prepare and improve the stability of a hydrophobic medication	Poor stability, post-dilution depolymerization

Table 3: Characteristics and classification of nano-drug carriers [100,101,102].

Transdermal Delivery

Patches:

Drug administration via transdermal approach: Effective at low plasma concentrations, low molecular mass, excessive lipid solubility, and high rate of first-pass metabolic activity [103].

A medicine placed transdermally to the skin in the form of an adhesive patch allows a certain amount to pass through the skin and into the bloodstream.

A controlled rate of drug delivery via skin layer penetration into the systemic circulations is achievable with the use of the transdermal drug delivery system.

Transdermal delivery, not only allows for the continuous release of drugs with short biological half-lives but also avoids pulsed entrance into the systemic circulation, frequently resulting in undesirable side effects [104].

Gels:

"Nanogel" describes chemically or physically produced nanoparticles of a cross-linked polymer [105].

Nanogels can absorb large amounts of either water or physiological fluid without changing the networks' inherent structure.

Using polymeric nanogel as a drug carrier offers multiple benefits, including a tendency to artificially regulate drug dosage through external stimuli, masking the unpleasant smell of the medicine, improving therapeutic efficacy, and reducing side effects [106]. Drug delivery systems or DDS aim to maximize the release of drugs, enhance solubility and bioavailability, limit drug toxicity and degradation, and exhibit strong adhesion because of van der Waals affinity. At the specific site of action, they release the active component in the precise dosage and proportion [107].

Oral Delivery Innovations

Solid Lipid Nanoparticles:

Drug administration methods based on lipids are being used more frequently to enhance the oral bioavailability of medications, with considerable success in raising the bioavailability of BCS class 2 medications. The primary reasons for an elevation in bioavailability include the drug's enhanced solubility, residence time, and lymphatic uptake [108]. Drug release can be modulated by using solid lipid nanoparticles (SLNs).

Dispersed physiological lipids in water or an aqueous surfactant solution create solid lipid nanoparticles, or SLNs, which are sub-micron colloidal carriers (50–1000 nm). They were first generated in the early 1990s [109].

Mucoadhesive Systems:

The phenomenon known as bioadhesion occurs when two components, preferably biological ones, adhere together for an extended duration due to interfacial forces. The mucoadhesion

mechanism occurs when the adhesive polymer contacts the mucous membrane. Mucoadhesive drug delivery systems (MDDS) are the equivalent drug delivery method.

There are several methods for administering drugs with MDDS, including the oral, buccal, nasal, pulmonary, gastrointestinal, vaginal, and rectal routes. It offers advantages over other formulations for the administration of proteins with a larger molecular weight and bioactives that are prone to instability and difficult to dose because of the wide range of delivery channels. Avoiding first-pass metabolism, better bioavailability, convenient administration, and longer residence periods are some benefits of MDDS that result in better therapeutic efficacy (Boddupalli *et al*., 2010; Alawdi & Solanki, 2021; Kumar *et al*., 2020).

The main aim is to treat heart-related conditions like angina pectoris, arrhythmias, and hypertension, the mucoadhesive buccal film came into existence (Jovanović *et al*., 2021).

Mucoadhesive buccal systems are one example of a novel drug delivery technique that can improve a medication's efficacy and bioavailability. Hepatic first-pass metabolism is prevented, when medications are delivered via mucoadhesive buccal delivery methods, increasing the bioavailability of drugs with limited oral bioavailability (Kumar *et al*. 2019).

Injectable Formulations:

Long-acting Injectables:

Possibly the first and only siRNA treatment that reduces LDL-C is Inclisiran. It is intended to be administered subcutaneously by a medical professional once, then again three months later, and then every six months thereafter. Inclisiran increases LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby stimulating LDL-C absorption by hepatocytes and lowering LDL-C levels in circulation [114].

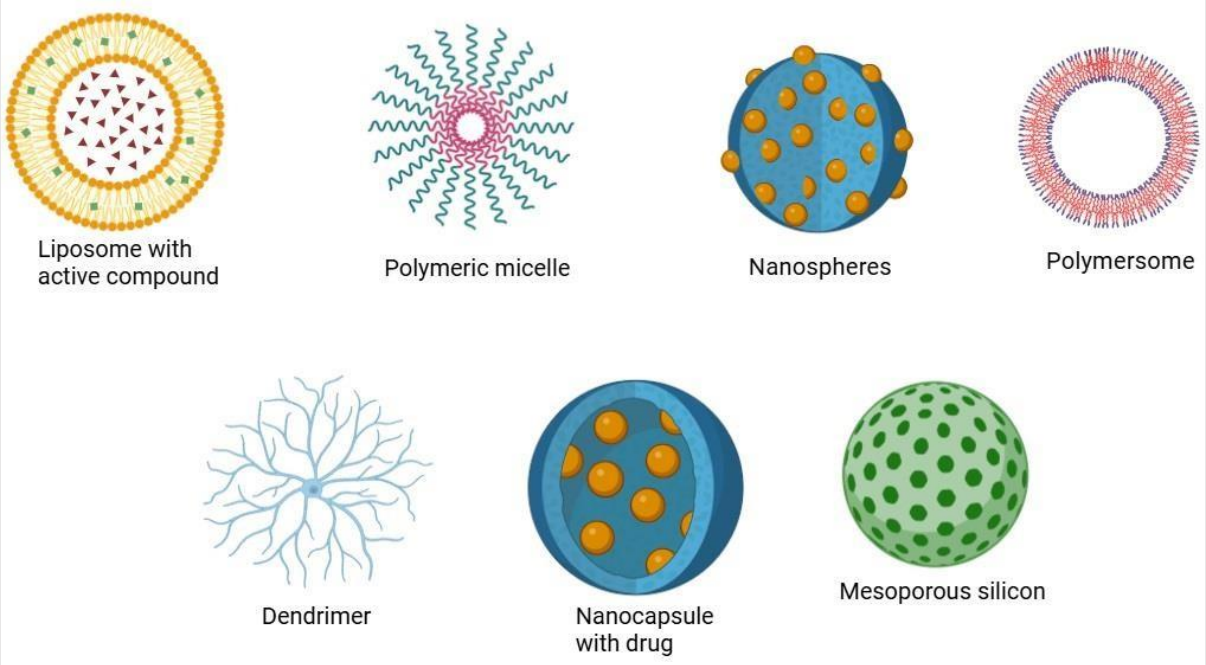

Figure 3: Various forms of nano drugs carriers

CHALLENGES IN DRUG DELIVERY

Poor Drug Bioavailability

Low Solubility:

Oral distribution of therapeutic agents is often limited by inadequate bioavailability and poor drug solubility. Nearly 40 percent of drugs generated recently have low solubility in water. Low drug solubility has prevented many treatments from reaching the market, although it plays a crucial role in medication formulation. These drugs also limit absorption and bioavailability.

One of the most commonly used techniques undergoing advancement currently is the development of nanocrystals, or nanosuspension (NS). The FDA classifies a medication as innovative when it is reformulated for NS.

A fundamental approach for improving the solubility of medications that are not readily soluble in water is nanotechnology. Because of their increased surface area and saturated solubility, these drugs' bioavailabilities and rates of dissolution may be enhanced by particle size reductions to the nanoscale [115]. Lipid-based formulations are suitable to deliver actives that are not easily soluble in water. Drug delivery systems that self-nano-emulsify (SNEDDS) are a potentially beneficial approach for faster and better absorption [116,117].

First-Pass Metabolism: The most widely used way of administering drugs is orally because of its accurate dosage, patient acceptance, cost-effective production technique, and prolonged

shelf life. Conventional tablets are normally linked to repeated daily dosing and unpredictable drug plasma concentration because of first-pass hepatic metabolism or gastrointestinal breakdown, which results in reduced bioavailability and brief duration of action [118].

Patients may benefit from innovative or alternative delivery routes or formulation modifications. For example, the benefits of sublingual or transdermal drug delivery include avoiding first-pass metabolism and being less painful (some painless techniques) [119].

Targeted Delivery

Other issues with RNA interference therapy that must be quickly addressed and improved to enable wide acceptance in the clinic include the risk of toxicity, targeting, time effect, and effective delivery mechanism of RNA (Navickas *et al*., 2016;).

To deal with delivery-related issues and completely fulfill the potential of RNAi-based therapies, it is necessary to use safe and effective nano-delivery systems. The liposome vector was designed to incorporate the apolipoprotein B (ApoB) siRNA (Zimmermann *et al*.,2006)**.**

A different study examined the impact of a transdermal delivery method. The generated nanotransfersomal carrier had major effects on hyperlipidemia without causing significant liver adverse effects, whereas pure atorvastatin showed no effect on lipid profile. However, atorvastatin nanotransfersomal substantially reduced LDL-C, triglycerides, and total cholesterol [122].

Particularly among the most widely used and effective medications in lipid-lowering therapy are (PCSK9) inhibitors. These compounds reduce the production or absorption of LDL and cholesterol and positively affect certain lipid metabolism pathways [123]. Yet, they also have negative side effects in addition to their advantageous multiple characteristics.

As a result, the purpose of targeted therapy is to lessen the dosage of drugs that reduce cholesterol and maintain an effect that is effective enough.

The distinct physicochemical characteristics of these nanoparticles have demonstrated potential drug delivery systems (DDS) to the intended bodily regions [124].

Controlled Release

To sustain therapeutic levels, it is vital to accomplish controlled medication release.

Controlling the active moiety's particle size, surface characteristics, and time of release to attain the expected proportion and dose of site-specific activity is the primary concern in developing NP as a DDS.

In contrast to different nanocarriers, polymeric NPs have several positive aspects, including improved controlled release features and better drug/protein stability [125].

Traditional tablets have a brief period of action and low bioavailability due to gastrointestinal breakdown and first-pass hepatic metabolism, which are frequently associated with repeated daily dosing and fluctuating medication plasma levels [126]. Sustained-release tablets offer a steady-state drug plasma level to increase the therapeutic efficacy of the drugs along with decreasing the toxicity associated with prolonged treatment [127]. In recent years, the use of bilayer or multilayer tablets for a combination of two or more drugs into a single dose form has increased. There are two different medication release patterns available with these tablets: immediate and sustained release.

PREVENTION AND PUBLIC HEALTH

Primary Prevention

Lifestyle Modification: Management for lipid metabolism disorders often involves lifestyle modifications (Malhotra *et al*., 2014). No matter what treatments are used, the most effectiveness can be accomplished by lowering the consumption of saturated fatty acids, mainly those derived from animals. Strict restrictions on alcoholic beverages and a decrease in consumption of quickly absorbed carbohydrates may drop triglyceride levels by more than 50%. Strict restrictions on alcoholic beverages and a decrease in consumption of readily absorbed carbohydrates may drop triglyceride levels by more than 50%. The lipid profile is also raised by regular physical activity.

Pharmacological Interventions: In lipid-lowering treatment, statins, Niemann-PickC1-like1 (NPC1L1) protein inhibitors, and PCSK9 inhibitors are some of the most efficient and often used medications. By affecting particular lipid metabolic pathways, such compounds decrease the synthesis or absorbing cholesterol and LDL [129].

Secondary Prevention

Screening Program: Understanding the variances and similarities among children and adolescents' risk categories, ages, genders, and ethnicities is crucial to fully appreciating the appropriateness, timeliness, and relevance of a broad population lipid screening. When compared to youths in good health, adolescents with increased TC levels had a five-fold higher chance of experiencing CVD events 40 years later [130]. The chance of cardiovascular death in both adult and pediatric patients may be reduced and CVD can be prevented with appropriate screening. To recognize hyperlipidemia in children and adolescents, several screening methods have been set up: A cascade method that screens from an index case to family members, a child-parent method that screens from children screened at a specific age to parents, a universal approach, a population screening program for certain ages, a selective method that evaluates a specific high-risk population, and a reverse cascade method that

examines pediatric affected patients to other family members. It is generally agreed upon that screening children is a universal screening method [131].

Monitor and Follow-Up:

Routine Lipid Screening: Some specialists have created guidelines for lipid screening, which involve conducting a "lipid profile" to check triglyceride and cholesterol levels. It is usually recommended that males aged 25 to 35 and females aged 45 to 35 undergo regular lipid screening [132]. For those at lesser risk, lipid screening should be performed every five years; as a patient's risk of cardiovascular disease increases, screening should be performed at regular intervals.

Public Health

Education: Patients suffering from hyperlipidemia should understand the possible implications of the condition and the way it affects their organs. It's mandatory to constantly talk about changing one's lifestyle, quitting smoking, and following a healthy diet. Discussing the positive attributes and drawbacks of each drug is essential before using it. Patients should receive information from their primary care physician and pharmacist about compliance with medications, adverse effects, interactions, and general hazards vs benefits of the prescribed medicine. The person receiving healthcare can often discuss with a dietitian or nutritionist if diet education is required.

While most participants were aware that inflammatory arthritis (IA) raises the risk of cardiovascular disease (CVD), they showed interest in figuring out more about the impact of arthritis on the heart and ways to lower their risk of CVD. Joining these focus groups offered some participants their initial education about their risk of CVD.

Community Programs: Peer coaches are individuals with the targeted condition who received training to support others with similar conditions following treatment recommendations from their physicians, building social support, and improving their self-efficacy, which translates into healthy behaviors [133]. The necessity of adopting personal responsibility was pointed out by the research participants who also indicated an interest in dietary practices, exercising, and managing stress as ways to lessen their risk of CVD. Respondents in all focus groups showed a keen interest in changing their lifestyles to reduce their cholesterol levels before beginning medication (e.g. statins).

Healthy Diet: For both adults and children, adopting dietary guidelines substantially decreases the risk of cardiovascular disease. Successful diet modifications can be accomplished with two distinctive basic strategies: a population approach and an individual plan [134]. The Individual method is a double-phase nutrition regimen that is customized for each patient. The first phase toward eliminating a child's cardiovascular risk is the Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1). It makes guidance similar to the population plan, which includes general guidelines for every child for managing blood

cholesterol and stopping atherosclerosis from developing [135,136]. Saturated fat intake should be limited to 7% of total calories and daily TC intake should be reduced to 200 mg, according to the Cardiovascular Health Integrated Lifestyle Diet-2 (CHILD-2) guidelines.

CLINICAL EVIDENCE AND TRIALS

Total Cholesterol

The anglo-scandinavian cardiac outcomes trial (ASCOT-LLA): Several investigations have shown a positive relationship between increased levels of total cholesterol and the incidence of stroke and CVD [137]. ASCOT-LLA, the Anglo-Scandinavian Cardiac Outcomes Trial, reported its findings of atorvastatin (10 mg), a lipid-lowering medication. Significant proportional decreases in cardiovascular events were found within a cohort of hypertension patients who, given certain risk factors, were, on average, at only modest cardiovascular risk and would not have been considered classically dyslipidemic [138].

The cholesterol and recurrent events trial (CARE): 4159 individuals with myocardial infarcts who had plasma total cholesterol levels below 240 mg per deciliter (mg/dL) and low-density lipoprotein (LDL) cholesterol levels between 115 and 174 mg per deciliter were studied in The Cholesterol and Recurrent Events (CARE) Trial. These patients had average cholesterol levels. These subjects were given either a placebo or 40 mg of pravastatin per day. According to study reports, several patients with coronary artery disease who had normal cholesterol levels benefited from taking cholesterol-lowering drugs [139].

(LDL) Low-density Lipoprotein

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT): Of the studies, 20 offered comprehensive LDL cholesterol data [140]. In almost all observational studies, but not all of them, lower LDL-C levels were shown to correlate with a lowered risk of ischemic stroke and CVD. According to the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), lowering LDL-C levels and lowering total cholesterol levels decreased the morbidity and mortality of coronary heart disease (CHD) in patients who were determined to be at high risk of the condition because of escalating LDL-C rates [141].

(HDL) High-density Lipoprotein

(Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) JUPITER trial: In a JUPITER trial evaluation, 314 CVD cases with controls (equal in age and gender), mean LDL (bad) cholesterol, and high levels of C-reactive protein were compared to 17,802 symptom-free patients. Research studies have revealed that of the four HDL biomarkers in correlation with cholesterol efflux capability in CVD, HDL particle

counts were the best reverse indication in patients receiving effective but non-baseline statin treatment. This is true for both baseline and statin investigations [142].

Improve-IT Trial, Ezetimibe: Ezetimibe has little or no side effects and is remarkably tolerable. Because ezetimibe blocks NPC1L1, it reduces the absorption of dietary cholesterol and cholesterol generated in bile [143]. The Improve-IT Trial, which screened people with ACS, discovered that ezetimibe when coupled with statin therapy, might reduce LDL-C levels from 1.8 to 1.4 mmol/L over seven years. Moreover, a 7% decrease in serious cardiovascular events was associated with this drop in LDL-C. However, individuals with diabetes showed a stronger manifestation of this effect [144]. According to clinical practice guidelines, Ezetimibe is advised as a secondary therapy preference [145]. It is usually given as a monotherapy in people who are unable to tolerate statins and as an adjuvant medication to help reach the desired LDL objectives.

(Canakinumab Anti-inflammatory Thrombosis Outcomes Study) CANTOS: The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), a multi-national study with 10,000 participants, was released in 2017, validating the inflammation hypothesis of atherothrombosis. In CANTOS, individuals on statins and other guideline-directed medical therapy demonstrated a significant 15–17% decrease in severe adverse cardiovascular consequences when they experienced narrow-spectrum targeting of interleukin-1β. However, blood pressure, apo B, and LDLC were not substantially reduced [146]. Furthermore, the greatest advantages within CANTOS were shown in individuals with the highest declines in hsCRP and interleukin-6, which is entirely compatible with the evolving assumption that "lower is also better for inflammation" [147]. Canakinumab has not been administered in cardiovascular therapy because of its dual capacity to suppress inflammation in the oncology setting.

(Colchicine Cardiovascular Outcomes trial) COLCOT: The publication of the COLCOT trial [148] in 2019, firmly supported the notion of the inflammation inhibition hypothesis; low-dose colchicine (0.5 mg po daily) has since been accepted as an efficient anti-inflammatory medication for the secondary prevention of atherosclerosis [149].

Microtubule inhibitors like colchicine with several anti-inflammatory actions, are frequently used in large dosages for a brief period to treat acute pericarditis and gout. has demonstrated a 31% reduction in significant cardiovascular problems in individuals with stable atherosclerosis [150] and 23% in individuals surviving from a recent myocardial infarction who are in the stable phase. Low-dose colchicine offers positive impacts that rise proportionately when treatment commences years after a preliminary atherosclerosis diagnosis, similar to how statins do. This states that anti-inflammatory medications lower the rate at which atherosclerotic plaque forms over time [151].

FUTURE DIRECTIONS IN PHARMACEUTICAL RESEARCH

Personalized Medicine: For a longer time since the only hyperlipidemic drugs available are statins with evident cardiovascular mortality benefits. Their purpose is to lower LDL cholesterol. Reducing lipids is intended to reduce bad cholesterol in high-risk individuals by 100 mg/dL.

Certain clinical trial studies illustrated how statins successfully reduced cardiovascular events after reducing LDL cholesterol levels.

However, in some cases, it was observed that many patients experienced statin intolerance. Previous data indicate that myopathy, which may arise from treatment discontinuity, is one of the negative effects of statin treatment. Still to treat LDL-C statins are mostly used but due to some barriers, they are among the failures. So, to overcome these problems some statins have shown that carriers can be used with the statins.

Further research on gene-related molecular pathways is conducted in pursuit of more effective treatments, and their impact on drugs that lower cholesterol would be better for successful treatments. A study was conducted to analyze the results of genetic variation causing statin metabolism and its relevance in personalized treatment. Statin efficacy (drug target and routes), toxicity to organs (developing myopathy pathways), and statin drug pharmacokinetics (carriers and metabolizing enzymes) are all influenced by several sets of significant genes.

Synthetic variants of statins are more likely to interact with HMG-CoA reductase due to their structural features. Furthermore, rosuvastatin has the strongest effect on lowering HMG-CoA reductase activity by up to 50% because of the polar contact between the methane sulphonamide group and the enzyme.

Rosuvastatin is a hydrophobic group and methane sulphonamide but due to some adverse effects like risk of myopathy and muscle toxicity problems. Statin is lacking in the successful treatment of hyperlipidemia. Moreover, attempts were made and studies were conducted to overcome the problem but after so many studies problems remained the same. According to reports, it is determined to create amorphous forms of statins because some of these medications have poor solubility and low bioavailability. This shows the potential to improve the solubility and bioavailability of statins while also improving their efficacy in treating cardiovascular diseases.

Pharmacogenomics (PGx) applications may improve drug selection, dosing, and monitoring in personalized medicine.

Although genetic evaluations are likely to increase the potency of statin therapy while preventing its negative consequences, they do not always forecast a reduction in the risk of cardiovascular events brought on by statins. Additionally, doctors can utilize the PGx test as a useful tool to track their patients' progress on statin therapy.

Pharmacogenetic testing has a higher chance of becoming a standard component of clinical practice in the future. Personalized medicine still faces challenges, and to overcome more studies are being done to modify and improve.

Novel Drug Delivery System: In contrast to conventional drug delivery, targeted drug delivery is a site-specific formulation that delivers the drug to the targeted location and at the exact location intended to treat the disease and exhibit better therapeutic benefits. The key goal of TDDS is to improve treatment effectiveness while reducing side effects by controlling and managing the pharmacokinetics, dynamics, aspecific toxicity, immunogenicity, and biorecognition of therapeutic agents.

TDDS differs from traditional DDS in this way, TDDS releases drugs at specific sites while the traditional one depends on the absorption of drugs via biological membranes affecting the drug's bioavailability and reducing its therapeutic impact.

The discovery of Nanotechnology was one of them in TDDS which is additionally called Novel Drug Delivery or Smart Drug Delivery and, was a good indication for the appearing problems from the conventional drug delivery. However, the challenges occurred because it was difficult to determine which target was appropriate for a certain illness state, a medicine that effectively cures the condition, how to administer the drug in a stable form to the targeted region, and how to avoid immunogenic and specific interactions. To overcome these challenges or difficulties, carriers are used mainly for drug reaching the target site, without affecting the non-target compartment, decreasing degradation of the drug molecule, minimizing side-effects, reducing drug quantity, improving patient compliance, increasing the drug concentration at the particular site, improved efficacy, controlled biodistribution, reducing toxicity, controlled release of drug.

To successfully carry the medication to the intended site, carriers—also known as vector entities—are needed. The drug is either dispersed or encapsulated in a medium. Polymeric materials, colloidals, Nanoparticles, and monoclonal antibodies are often employed carriers. The carrier to be employed depends on the disease condition, the desired location, and the nature of the drugs. An effective and safe nano-delivery method for treating CVD is RNAi-based therapy. Within 24 hours of treatment, the liposome vector containing the apolipoprotein B (ApoB) siRNA, reduced the concentration of bad cholesterol and cholesterol.

Several pharmaceutical companies developed new nano dosages that deliver siRNA to the desirable cells at the right time. Nanomaterials can be administered orally, transdermally, and by other channels, including the respiratory, digestive, and skin systems. According to certain research, these materials may enter the bloodstream through these mucous membranes. Additionally, it has been found that the inflammatory reactions triggered by nanomaterials can influence the emergence and progression of cardiovascular diseases, or CVDs, such as myocardial infarction, cardiac arrest, and hypertension. Based on reports, carriers can travel

via the blood to all organs if they are not removed on time. This might cause the body to release some inflammatory cytokines and eventually result in cytotoxicity, which raises the possibility of cardiovascular problems. Compiling all of the research and information, on the toxicity that nanoparticles produce to the cardiovascular system's mechanisms worldwide is still in its early stages. To stop, prevent, or lessen any potential negative health consequences, scientists must therefore continue their studies and research on the detrimental impact on the cardiovascular system as well as the mechanism of nanomaterials that can be used more effectively and have good effects. The field of nanomedicine must find a solution to the degradation of products and the biocompatibility of particles loaded with nanodrugs in the future. With some creativity and in-depth research into the molecular pathological mechanism of CVDs, new techniques and methods will be promoted for clinical diagnosis and therapy.

Combination Therapy: A new class of medication known as PCSK9 inhibitors has recently been approved for the medical treatment of hyperlipidemia, particularly in patients with FH, those at high risk of cardiovascular events, and those whose LDL cholesterol main target for reduction fails to be achieved even after taking the maximum dosage of statins. Hepatocytes produce the protein PCSK9, which binds to the surface of liver cell LDL receptors to lessen the liver's capacity to eliminate LDL-C from circulation and encourage its breakdown.

Monoclonal antibodies particularly associated with circulating PCSK9, alirocumab, and evolocumab block its interaction with LDL receptors. By restricting the PCSK9 protein, these monoclonal antibodies retain the hepatocytes' surface LDL receptors and improve their capacity to extract LDL cholesterol from the bloodstream. Evolocumab and alirocumab combined with statin therapy have been shown in clinical trials to lower LDL-C by 60% to 70%, which is considerably better than taking a statin drug alone. These reductions are safe and well-tolerated.

Additionally, in high-risk patients, PCSK9 inhibitors have been shown to reduce the incidence of cardiovascular events such as myocardial infarction and strokes. PCSK9 inhibitors are well tolerable drugs and in correspondence safe to use. Still, information is being gathered mainly regarding potential negative effects on immunogenicity, neurocognitive functioning, and liver function in the safety measures.

Due to its lipid-lowering and anti-inflammatory properties, Gemcaebene, an oral lipid-lowering medication with a fixed dosage, is likely to be used in conjunction with statins for patients with FH or together with other lipid-reducing drugs for those with hypertriglyceridemia and non-alcoholic fatty liver disease.

In addition to raising the breakdown and elimination of lipoproteins from blood, gemcaebene blocks the hepatic lipid synthesis of Apolipoprotein C-III (Apo C-III) and lowers Apo C-III levels. It also activates peroxisome proliferator-activated receptor alpha (PPAR-α), which increases fatty acid oxidation and helps reduce triglyceride concentrations in the blood and

liver. It has also been shown to lower levels of pro-inflammatory cytokines, which has significant advantages in inflammatory conditions like non-alcoholic fatty liver disease.

It showed that daily dosages of 300 and 900 mg reduced levels of bad cholesterol by 23% and 28%, respectively when taken with statins. But still, clinical trials have illustrated, that there is a lack of efficiency and safety as it is for the brief. Therefore, more research is being done to verify the long-lasting safety advantages and best practices.

CONCLUSION

Hyperlipidemia is a severe health issue that is a life-threatening condition thus contributing to cardiovascular diseases. This review demonstrates the pathophysiology of hyperlipidemia and risk factors related to it. It also highlights the recent advancements in lipid-lowering drugs which involve novel drugs, and genetic testing for better results. To manage the condition lifestyle modification along with pharmacotherapy is required. Most importantly, considering the patient's education and raising awareness for the disease by the healthcare provider can lower the chances of cardiovascular diseases and help the patient control their lipid levels.

Innovation in drug delivery, like nanotechnology, provides enhanced treatment results. Nanotechnology as a controlled drug delivery method revealed certain benefits in the therapy of CVDs, remarkably tackling problems like controlled release and sustained release while decreasing the drug's toxicity level.

Research is still in the process of overcoming the challenges of novel and conventional drugs faced during the therapy trial. Additionally, the study is going on for the NDDS to solve problems like the biocompatibility of loaded drugs and the deterioration of products, which need to be resolved from a future perspective.

Acknowledgment

No acknowledgment

Funding

None

Conflict of Interest

The authors declare no conflict of interest

Author Contribution:

Richa Chandra.: Conceptualization, Methodology, Software, Writing- Review & Editing; Kalpana Kushwaha.: Supervision, Data curation, Writing- Original draft preparation, Validation; Pratima Katiyar.: Visualization, Investigation

REFERENCES

1. Goodman Gilman. Eds. The pharmacological basis of therapeutics. Macmillan Publishing Company, New York; 1970

2. Hassan B. Overview on Hyperlipidemia. J Chromat Separation Techniq, 2013; 4:2.

3. Dhuley J, Naik SR, Rele S, Banerji A. Pharm Pharmacol Commun,1999; 5:689.

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

5. Onwe, P. E.; Folawiyo, M. A.; Anyigor-Ogah, C. S.; Umahi, G.; Okorocha, A. E.; and Afoke, A. (2015): Hyperlipidemia: etiology and possible control. IOSR J. Dent. Med. Sci, 14: 93-100

6. Lipman TH, Hayman LL, Fabian CV, DiFazio DA, Hale PM, Goldsmith BM, et al. Risk factors for cardiovascular disease in children with type I diabetes. Nurs Res 2000;49:160-166.

7. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. Bmj. 2008;337.

8. S. Karr, "Epidemiology and management of hyperlipidemia," The American Journal of Managed Care, vol. 23, 9 Supplement, pp. S139–S148, 2017

9. P. Libby, J. E. Buring, L. Badimon et al., "Atherosclerosis," Nature Reviews Disease Primers, vol. 5, no. 1, 2019.

10. Amal Umran Mosa, Iman Hussein Naser, Zahraa Abd Alkareem et al. Hyperlipidemia: pathophysiology, causes, complications, and treatment. Kerbala journal of pharmacy and pharmaceutical science 01/07/2021 A review 3

11. Folawiyo MA., Anyigor-Ogah CS., Umahi G., Okorocha AE, Afoke AO et al. Hyperlipidemia: Etiology and Possible Control. Journal of Dental and Medical Sciences 2015: 14(10) ; 93-100

12. Natesan V., Kim S. J. Diabetic nephropathy - a review of risk factors, progression, mechanism, and dietary management. *Biomol. Ther. (Seoul)* 2021;29:365–372.

13. Verma N. Introduction to hyperlipidemia and its treatment: a review. *Int. J. Curr. Pharm. Res.* 2017;9:6–14.

14. Haake, D.A.; Zückert, W.R. Spirochetal Lipoproteins in Pathogenesis and Immunity. Curr. Top. Microbiol. Immunol. 2018, 415, 239–271.

15. Chiou, K.-R.; Charng, M.-J. Common mutations of familial hypercholesterolemia patients in Taiwan: Characteristics and implications of migrations from southeast China. Gene 2012, 498, 100–106.

16. Slack, J. Risks of Ischaemic Heart-Disease in Familial Hyperlipoproteinaemic States. Lancet 1969, 2, 1380–1382.

17. Stone, N.J.; Levy, R.I.; Fredrickson, D.S.; Verter, J. Coronary Artery Disease in 116 Kindred with Familial Type II Hyperlipoproteinemia. Circulation 1974, 49, 476–488.

18. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992, 89, 495–501.

19. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics 2011, 128 (Suppl. S5), S213–S256.

20. Lobelo, F.; Muth, N.D.; Hanson, S.; Nemeth, B.A.; LaBella, C.R.; Brooks, M.A.; Canty, G.; Diamond, A.B.; Hennrikus, W.; Logan, K.; et al. Physical Activity Assessment and Counseling in Pediatric Clinical Settings. Pediatrics 2020, 145, e20193992.

21. West, S.L.; Banks, L.; Schneiderman, J.E.; Caterini, J.E.; Stephens, S.; White, G.; Dogra, S.; Wells, G.D. Physical Activity for Children with Chronic Disease; a Narrative Review and Practical Applications. BMC Pediatr. 2019, 19, 12.

22. Drewnowski A, Darmon N. The economics of obesity: dietary energy density and energy cost. Am J Clin Nutr 2005;82:265S-73S.

23. Du S, Mroz TA, Zhai F, Popkin BM. Rapid income growth adversely affect diet quality in China- particularly for the poor! Soc Sci Med 2004;59:1505-15.

24. Huang, M.; Zheng, J.; Chen, L.; You, S.; Huang, H. Role of apolipoproteins in the pathogenesis of obesity. Clin. Chim. Acta Int. J. Clin. Chem. 2023, 545, 117359.

25. Wattigney, W.A.; Harsha, D.W.; Srinivasan, S.R.; Webber, L.S.; Berenson, G.S. Increasing Impact of Obesity on Serum Lipids and Lipoproteins in Young Adults. The Bogalusa Heart Study. Arch. Intern. Med. 1991, 151, 2017–2022.

26. Kavey, R.-E.W.; Allada, V.; Daniels, S.R.; Hayman, L.L.; McCrindle, B.W.; Newburger, J.W.; Parekh, R.S.; Steinberger, J.; American Heart Association Expert Panel on Population and Prevention Science; American Heart Association Council on Cardiovascular Disease in the Young; et al. Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular

Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Circulation 2006, 114, 2710–2738.

27. Lippi, G.; Targher, G.; Salvagno, G.L.; Montagnana, M.; Franchini, M.; Guidi, G.C. Lipoproteins (a) and ageing. Clin. Lab. 2010, 56, 463–466.

28. Ferguson TS, Younger NO, Tulloch-Reid MK, Wright MB, Ward EM, Ashley DE, et al. Prevalence of prehypertension and its relationship to risk factors for cardiovascular disease in Jamaica: analysis from a cross-sectional survey. BMC cardiovascular disorders. 2008;8:20.

29. Hosey GM, Samo M, Gregg EW, Padden D, Bibb SG. Socioeconomic and demographic predictors of selected cardiovascular risk factors among adults living in Pohnpei, Federated States of Micronesia. BMC Public Health. 2014;14(1):895.

30. Pilic L, Pedlar CR, Mavrommatis Y. Salt-sensitive hypertension: mechanisms and effects of dietary and other lifestyle factors. Nutrition reviews. 2016;74(10):645–58.

31. Wilson MD, Conroy LM, Dorevitch S. Occupational stress and subclinical atherosclerosis: a systematic review. International journal of occupational and environmental health. 2014;20(4):271–80.

32. Finney C, Stergiopoulos E, Hensel J, Bonato S, Dewa CS. Organizational stressors associated with job stress and burnout in correctional officers: a systematic review. BMC Public Health. 2013;13:82. Epub 2013/01/30.

33. J. P. Halcox, J. R. Banegas, C. Roy et al., "Prevalence and treatment of atherogenic dyslipidemia in the primary prevention of cardiovascular disease in Europe: EURIKA, a cross-sectional observational study," BMC Cardiovascular Disorders, vol. 17, no. 1, 2017.

34. Vijayaraj PS, Muthukumar K, Sabarirajan J, Naciappan V. Indian Journal of Biochemistry and biophysics, 2011; 48:54-58.

35. Davey Smith G and Pekkanen J. Br Med J, 1992; 304:431-440

36. Amit G, Vandana S, Sidharth M. HYPERLIPIDEMIA: An Updated Review. Inter J of Biopharma & Toxicol Res 2011;1:81-89.

37. Shattat GF. A review article on hyperlipidemia: types, treatments and new drug targets. Biomedical and pharmacology journal. 2015;7(1):399-409

38. Reitsma, S.; Slaaf, D.W.; Vink, H.; van Zandvoort, M.A.M.J.; Oude Egbrink, M.G. The endothelial glycocalyx: Composition, functions, and visualization. *Pflug. Arch. Eur. J. Physiol.* 2007, *454*, 345–359.

39. A Review Article on Hyperlipidemia: Types, Treatments and New Drug Targets GHASSAN F. SHATTAT College of Science and Health Professions, King Saud Bin Biomedical & Pharmacology Journal 2014; 7(2), 399-409

40. Niharika Verma. Introduction to hyperlipidemia and its treatment: a review. Int J Curr Pharm Res 2016; 9(1): 6- 14

41. 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.

42. 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.

43. 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.

44. Kullo IJ, Rooke TW. CLINICAL PRACTICE. Peripheral Artery Disease. N Engl J Med. 2016;374:861–871.

45. Nickolas TL, Radhakrishnan J, Appel GB et al. Hyperlipidemia and thrombotic complications in patients with membranous nephropathy. Semin Nephrol 2003; 23: 406-11.

46. Coskun A, Erkan N, Yakan S, Yildirim M, Carti E, Ucar D, et al. Treatment of hypertriglyceridemia-induced acute pancreatitis with insulin. Gastroenterol Rev. 2015;1:18–22.

47. Baranyai T, Terzin V, Vajda Á, Wittmann T, Czakó L. Hypertriglyceridemia causes more severe course of acute pancreatitis. Clin Lipidol. 2012 Dec 1;7(6):731–6.

48. Sarac S, Atamer A, Atamer Y, Can AS, Bilici A, Tacyildiz I, et al. Leptin levels and lipoprotein profiles in patients with cholelithiasis. J Int Med Res. 2015; 43:385–92

49. Harish B. A cross sectional study on causes and risk factors of gallstone disease among patients with symptomatic cholelithiasis. Int J Nurs Res Pract 2014;1:20-4.

50. Channa NA, Khand F, Ghanghro AB, Soomro AM. Quantitative analysis of serum lipid profile in gallstone patients and controls. Pak J Anal Environ Chem 2010;11:59-65.

51. Edeoga HO, Okwu DE, Mbaebie BO. Phytochemical constituents of some Nigerian medicinal plants. African journal of biotechnology. 2005 Aug 19;4(7):685-8.

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

53. Fredrickson DS. An international classification of hyperlipidemias and hyperlipoproteinemias. Ann Intern Med. 1971 Sep;75(3):471-2.

54. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. Am J Cardiol. 2012 Sep 15;110(6):823-5.

55. Fiorentino, R.; Chiarelli, F. Treatment of Dyslipidaemia in Children. Biomedicines 2021, 9, 1078.

56. Delgado-Lista, J.; Alcala-Diaz, J.F.; Torres-Peña, J.D.; Quintana-Navarro, G.M.; Fuentes, F.; Garcia-Rios, A.; Ortiz-Morales, A.M.; Gonzalez-Requero, A.I.; Perez-Caballero, A.I.; Yubero-Serrano, E.M.; et al. Long-Term Secondary Prevention of Cardiovascular Disease with a Mediterranean Diet and a Low-Fat Diet (CORDIOPREV): A Randomised Controlled Trial. Lancet 2022, 399, 1876–1885.

57. Estruch R., Ros E., Salas-Salvadó J., Covas M. I., Corella D., Arós F., Gómez-Gracia E., Ruiz-Gutiérrez V., Fiol M., Lapetra J., Lamuela-Raventos R. M., Serra-Majem L., Pintó X., Basora J., Muñoz M. A., Sorlí J. V., Martínez J. A., Martínez-González M. A. Primary prevention of cardiovascular disease with a mediterranean diet. *N Engl J Med.* 2013;368:1279–1290.

58. Wu L., Piotrowski K., Rau T., Waldmann E., Broedl U. C., Demmelmair H., Koletzko B., Stark R. G., Nagel J. M., Mantzoros C. S., Parhofer K. G. Walnut-enriched diet reduces fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: a randomized controlled cross-over clinical trial. *Metabolism.* 2014;63:382–391.

59. Hegele R. A., Ginsberg H. N., Chapman M. J., Nordestgaard B. G., Kuivenhoven J. A., Averna M., Borén J., Bruckert E., Catapano A. L., Descamps O. S., Hovingh G. K., Humphries S. E., Kovanen P. T., Masana L., Pajukanta P., Parhofer K. G., Raal F. J., Ray K. K., Santos R. D., Stalenhoef A. F., Stroes E., Taskinen M. R., Tybjærg-Hansen A., Watts G. F., Wiklund O. European Atherosclerosis Society Consensus Panel, author. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol.* 2014;2:655–666.

60. Lobelo, F.; Muth, N.D.; Hanson, S.; Nemeth, B.A.; LaBella, C.R.; Brooks, M.A.; Canty, G.; Diamond, A.B.; Hennrikus, W.; Logan, K.; et al. Physical Activity Assessment and Counseling in Pediatric Clinical Settings. Pediatrics 2020, 145, e20193992.

61. West, S.L.; Banks, L.; Schneiderman, J.E.; Caterini, J.E.; Stephens, S.; White, G.; Dogra, S.; Wells, G.D. Physical Activity for Children with Chronic Disease; a Narrative Review and Practical Applications. BMC Pediatr. 2019, 19, 12.

62. Hind, K.; Burrows, M. Weight-Bearing Exercise and Bone Mineral Accrual in Children and Adolescents: A Review of Controlled Trials. Bone 2007, 40, 14–27.

63. Fiorentino, R.; Chiarelli, F. Treatment of Dyslipidaemia in Children. Biomedicines 2021, 9, 1078.

64. LeBlanc, A.G.; Janssen, I. Dose-Response Relationship between Physical Activity and Dyslipidemia in Youth. Can. J. Cardiol. 2010, 26, e201–e205.

65. Piercy, K.L.; Troiano, R.P.; Ballard, R.M.; Carlson, S.A.; Fulton, J.E.; Galuska, D.A.; George, S.M.; Olson, R.D. The Physical Activity Guidelines for Americans. JAMA 2018, 320, 2020.

66. Stewart, Jeremy, et al. "Hyperlipidemia." *Pediatrics in review* 41.8 (2020): 393-402.

67. Stewart, J., McCallin, T., Martinez, J., Chacko, S., & Yusuf, S. (2020). Hyperlipidemia. *Pediatrics in review*, *41*(8), 393-402.

68. Franco M, Cooper RS, Bilal U, Fuster V. Challenges and opportunities for cardiovascular disease prevention. Am J Med 2011;124:95-102.

69. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596-616.

70. Stewart, J., McCallin, T., Martinez, J., Chacko, S. and Yusuf, S., 2020. Hyperlipidemia. *Pediatrics in review*, *41*(8), pp.393-402.

71. Fiorentino R. and Chiarelli F., Treatment of dyslipidaemia in children, *Biomedicines*. (2021) 9, no. 9,

72. Stewart J, McCallin T, Martinez J, Chacko S, Yusuf S. Hyperlipidemia. Pediatrics in review. 2020 Aug 1;41(8):393-402.

73. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT., ESC Scientific Document Group. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016 Oct 14;37(39):2999-3058.

74. Fiorentino R. and Chiarelli F., Treatment of dyslipidaemia in children, *Biomedicines*. (2021) 9, no. 9,

75. Ballantyne CM, Grundy SM, Oberman A, Kreisberg RA, Havel RJ, Frost PH, Haffner SM. Hyperlipidemia: diagnostic and therapeutic perspectives. J Clin Endocrinol Metab. 2000 Jun;85(6):2089-112.

76. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. Am J Cardiol. 2012 Sep 15;110(6):823-5.

77. Framingham Heart Study. Cardiovascular disease (10-year risk). Accessed February 14, 2023.

78. Vinson A, Guerra L, Hamilton L, Wilson DP. Fnla. Reverse Cascade Screening for Familial Hypercholesterolemia. J Pediatr Nurs. 2019;44:50–55.

79. Chhetry M, Jialal I et al. Lipid-Lowering Drug Therapy. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024

80. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. 2004;43:2142–2146.

81. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans

Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999; 341(6): 410-8.

82. Wang D, Liu B, Tao W, Hao Z, Liu M et al. Fibrates for secondary prevention of cardiovascular disease and stroke. Cochrane Database Syst 2015; (10): CD009580.

83. Probstfield JL, Hunninghake DB et al. Nicotinic acid as a lipoprotein-altering agent. Therapy directed by the primary physician. Arch Intern Med. 1994 Jul 25; 154(14): 1557-9

84. FDA clears bempedoic acid non-statin LDL-cholesterol lowering drug. [Jul;2021];

85. Handelsman Y. Role of bile acid sequestrants in the treatment of type 2 diabetes. Diabetes Care. 2011 May;34 Suppl 2(Suppl 2): S244-50.

86. Mazidi, M.; Rezaie, P.; Karimi, E.; and Kengne, A. P. (2017): The effects of bile acid sequestrants on lipid profile and blood glucose concentrations: a systematic review and meta-analysis of randomized controlled Int. J. Cardiol, 227: 850-857.

87. Martin B, G.; and MBHickey, D. (1994): Bile acid sequestrants. Expert Opin Investig Drugs, 3: 493-500.

88. Tonstad, S.; Knudtzon, J.; Sivertsen, M.; Refsum, H.; and Ose, L. (1996): Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. J. Pediatr, 129: 42-49.

89. Steinmetz, K. L.; and Schonder, K. S. (2005): Colesevelam: potential uses for the newest bile resin. Cardiovasc. Drug Rev, 23: 15-30.

90. Waller J. R., Waller D. G. Drugs for lipid disorders, antiplatelet drugs and fibrinolytics. *Medicine.* 2014;42:544–548.

91. Dias S., Paredes S., Ribeiro L. Drugs involved in dyslipidemia and obesity treatment: focus on adipose tissue. *Int. J. Endocrinol.* 2018;4:2637418.

92. Maurya, A.; Singh, A.K.; Mishra, G.; Kumari, K.; Rai, A.; Sharma, B.; Kulkarni, G.T.; Awasthi, R. Strategic use of nanotechnology in drug targeting and its consequences on human health: A focused review. Interv. Med. Appl. Sci. 2019, 11, 38–54.

93. Sharma, K.; Kumar, K.; Mishra, N. Nanoparticulate carrier system: A novel treatment approach for hyperlipidemia. Drug Deliv. 2016, 23, 684–699.

94. Landesman-Milo, D., Goldsmith, M., Leviatan, B. S., Witenberg, B., Brown, E., Leibovitch, S., et al. (2013). Hyaluronan grafted lipid-based nanoparticles as RNAi carriers for cancer cells. Cancer Lett. 334, 221–227.

95. Yingchoncharoen, P., Kalinowski, D. S., and Richardson, D. R. (2016). Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. Pharmacol. Rev. 68, 701–787.

96. Ou, L.C.; Zhong, S.; Ou, J.S.; Tian, J.W. Application of targeted therapy strategies with nanomedicine delivery for atherosclerosis. Acta Pharmacol. Sin. 2021, 42, 10–17.

97. Katsuki, S.; Matoba, T.; Koga, J.I.; Nakano, K.; Egashira, K. Anti-inflammatory Nanomedicine for Cardiovascular Disease. Front. Cardiovasc. Med. 2017, 4, 87.

98. W.Zhao,X.Jin, Y. Cong, Y. Liu, J. Fu, Degradable natural polymer hydrogels for articular cartilage tissue engineering, J. Chem. Technol. Biotechnol. 88 (2013) 327–339

99. MicroMedex. "DRUGDEX® (2008), Evaluations—Niacin". New Hersey: Thomson Healthcare.

100. Jain, A., and Jain, S. K. (2018). Stimuli-responsive smart liposomes in cancer targeting. Curr. Drug Targets 19, 259–270.

101. Elsabahy, M., and Wooley, K. L. (2012). Design of polymeric nanoparticles for biomedical delivery applications. Chem. Soc. Rev. 41, 2545–2561.

102. Cagel, M., Tesan, F. C., Bernabeu, E., Salgueiro, M. J., Zubillaga, M. B., Moretton, M. A., et al. (2017). Polymeric mixed micelles as nanomedicines: achievements and perspectives. Eur. J. Pharm. Biopharm. 113, 211–228.

103. Mark R. Prausnitzand Robert LangerNatBiotechnol, Transdermal drug delivery, Nat Biotechnol. 2008 26(11): 1261–1268.

104. Sandhya rani Mandadi, Vishwanadhamyerraguntaformulation and evaluation of atorvastatin calcium sustained release tablets, 2006, 6(3):124-130 ·

105. Ghaywat, S.D.; Mate, P.S.; Parsutkar, Y.M.; Chandimeshram, A.D.; Umekar, M.J. Overview of nanogel and its applications. GSC Biol. Pharm. Sci. 2021, 16, 040–061.

106. Cuggino, J.C.; Blanco, E.R.; Gugliotta, L.M.; Igarzabal, C.I.; Calderón, M. Crossing biological barriers with nanogels to improve drug delivery performance. J. Control. Release 2019, 307, 221–246.

107. Sharma, A.; Garg, T.; Aman, A.; Panchal, K.; Sharma, R.; Kumar, S.; Markandeywar, T. Nanogel—An advanced drug delivery tool: Current and future. Artif. Cells Nanomed. Biotechnol. 2016, 44, 165–177.

108. Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. *J Pharm Sci.* 1993;82:979–87.

109. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery: A review of the state of the art. *Eur J Pharm Biopharm.* 2000;50:161–77.

110. Boddupalli, B.M., Mohammed, Z.N., Nath, R.A. and Banji, D., (2010). Mucoadhesive drug delivery system: An overview. J. Adv. Pharm. Technol. Res,1(4), p.381.

111. Alawdi, S. and Solanki, A.B.,(2021). Mucoadhesive drug delivery systems: A review of recent developments. Int. J. Biol. Sci., 2(1),50-64.

112. Jovanović M, Tomić N, Cvijić S, Stojanović, D., Ibrić, S. and Uskoković, P., (2021). Mucoadhesive gelatin buccal films with propranolol hydrochloride: Evaluation of mechanical, mucoadhesive, and biopharmaceutical properties. Pharma ceutics.,13(2):273

113. Kumar, A M et al. 2019. "A Review on Mucoadhesive Drug Delivery Systems." Research Journal of Pharmaceutical Dosage Forms and Technology 11(4): 280–87.

114. K. K.Ray, R. S. Wright, D. Kallend et al., "Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol," New England Journal of Medicine, vol. 382, no. 16, pp. 1507–1519, 2020.

115. Deshkar, S.S.; Sonkamble, K.G.; Mahore, J.G. Formulation and Optimization of Nanosuspension for Improving Solubility and Dissolution of Gemfibrozil. Asian J. Pharm. Clin. Res. 2019, 12, 157–163.

116. Hong, J.Y.; Kim, J.K.; Song, Y.K.; Park, J.S.; Kim, C.K. A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption. J. Control. Release 2006, 110, 332–338.

117. Singh, S.K.; Verma, P.R.P.; Razdan, B. Development and characterization of a lovastatin loaded self-microemulsifying drug delivery system. Pharm. Dev. Technol. 2010, 15, 469–483.

118. Alqahtani, M.S.; Kazi, M.; Alsenaidy, M.A.; Ahmad, M.Z. Advances in oral drug delivery. Front. Pharm. 2021, 12, 618411.

119. Brown MB, Martin GP, Jones SA, Akomeah FK. Dermal and transdermal drug delivery systems: current and future prospects. Drug Deliv J Deliv Target Ther Agents. 2006;13:175–87.

120. Navickas, R., Gal, D., Laucevi Ius, A., Taparauskait, A., Zdanyt, M., and Holvoet, P. (2016). Identifying circulating microRNAs as biomarkers of cardiovascular disease: a systematic review. Cardiovasc. Res. 111, 322–337.

121. Zimmermann, T. S., Lee, A. C. H., Akinc, A., Bramlage, B., Bumcrot, D., Fedoruk, M. N., et al. (2006). RNAi-mediated gene silencing in non-human primates. Nature 441, 111–114.

122. Mahmoud, M.O.; Aboud, H.M.; Hassan, A.H.; Ali, A.A.; Johnston, T.P. Transdermal delivery of atorvastatin calcium from novel nanovesicular systems using polyethylene glycol fatty acid esters: Ameliorated effect without liver toxicity in poloxamer 407-induced hyperlipidemic rats. J. Control Release 2017, 254, 10–22.

123. Li, H.; Jing, X.; Deng, X.; Ouyang, D. Targets of anti-hyperlipidemia drugs. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2013, 38, 101–108. (In Chinese)

124. Ludwig, A.The use of mucoadhesive polymers in ocular drug delivery. Adv. Drug Deliv. Rev. 2005, 57, 1595–1639.

125. Xu, H.; Xu, X.; Li, S.; Song, W.-L.; Yu, D.-G.; Annie Bligh, S.W. The Effect of Drug Heterogeneous Distributions within Core-Sheath Nanostructures on Its Sustained Release Profiles. Biomolecules 2021, 11, 1330.

126. Ansel, H.C.; Popovich, N.G.; Allen, L.V., Jr. Ansel's Pharmaceutical Dosage Forms Drug Delivery Systems

127. Abebe, A.; Akseli, I.; Sprockel, O.; Kottala, N.; Cuitiño, A.M. Review of bilayer tablet technology. Int. J. Pharm. 2014, 461, 549–558.

128. Malhotra A., Shafiq N., Arora A., Singh M., Kumar R., Malhotra S. Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolaemia. *Cochrane Database Syst. Rev.* 2014;2014:CD001918.

129. Li, H.; Jing, X.; Deng, X.; Ouyang, D. Targets of anti-hyperlipidemia drugs. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2013, 38, 101–108. (In Chinese)

130. Kwiterovich, P.O. Recognition and Management of Dyslipidemia in Children and Adolescents. J. Clin. Endocrinol. Metab. 2008, 93, 4200–4209.

131. Mainieri, F.; Tagi, V.M.; Chiarelli, F. Recent Advances on Familial Hypercholesterolemia in Children and Adolescents. Biomedicines 2022, 10, 1043.

132. Fredrickson DS. An international classification of hyperlipidemias and hyperlipoproteinemias. Ann Intern Med. 1971 Sep;75(3):471-2.

133. Franklin BA, Brubaker P, Harber MP, Lavie CJ, Myers J, Kaminsky LA. The Journal of Cardiopulmonary Rehabilitation and Prevention at 40 yr and Its Role in Promoting Preventive Cardiology: Part 2. J Cardiopulm Rehabil Prev. 2020 Jul;40(4):209-214.

134. Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis. 2015;74(2):326–32.

135. Zullig LL, Melnyk SD, Stechuchak KM, et al. The cardiovascular intervention improvement telemedicine study (CITIES): rationale for a tailored behavioral and educational pharmacist-administered intervention for achieving cardiovascular disease risk reduction. Telemed J E-Health. 2014;20(2):135–43.

136. Corkins, M.R.; Daniels, S.R.; de Ferranti, S.D.; Golden, N.H.; Kim, J.H.; Magge, S.N.; Schwarzenberg, S.J. Nutrition in Children and Adolescents. Med. Clin. North Am. 2016, 100, 1217–1235.

137. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;**360**(9326):7–22.

138. Sever P.S., Dahlöf B., Poulter N.R., Wedel H., Beevers G., Caulfield M., Collins R., Kjeldsen S.E., Kristinsson A., McInnes G.T., Mehlsen J., Nieminen M., O'Brien E., Ostergren J. ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;**361**(9364):1149–1158.

139. Sacks F.M., Pfeffer M.A., Moye L.A., Rouleau J.L., Rutherford J.D., Cole T.G., Brown L., Warnica J.W., Arnold J.M., Wun C.C., Davis B.R., Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels.

Cholesterol and Recurrent Events Trial investigators. *N. Engl. J. Med.* 1996;**335**(14):1001–1009.

140. Collaboration P.S. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. *Lancet.* 1995;**346**(8991-8992):1647–1653.

141. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA.* 1984;**251**(3):351–364.

142. Khera A.V., Demler O.V., Adelman S.J., Collins H.L., Glynn R.J., Ridker P.M., Rader D.J., Mora S. Cholesterol Efflux Capacity, High-Density Lipoprotein Particle Number, and Incident Cardiovascular Events: An Analysis From the JUPITER Trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). *Circulation.* 2017;**135**(25):2494–2504.

143. Maximizing the benefits of cholesterol-lowering drugs. Feingold KR. *Curr Opin Lipidol.* 2019;30:388–394.

144. Ezetimibe added to statin therapy after acute coronary syndromes. Cannon CP, Blazing MA, Giugliano RP, et al. *N Engl J Med.* 2015 ;372:2387–2397.

145. Pearson GJ, Thanassoulis G, Anderson TJ, et al. *Canadian J Cardiol.* Vol. 37. W; 2021. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults; pp. 1129–1150

146. P.M. Ridker, B. Everett, T. Thuren, for the CANTOS Trial Group, et al., Anti-inflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.

147. P. Ridker, P. Libby, MacFadyen, et al., Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab anti-inflammatory thrombosis outcomes study (CANTOS), Eur. Heart J. 39 (2018) 3499–3507.

148. J.C. Tardif, S. Kouz, D.D. Waters, et al., Efficacy and safety of low-dose colchicine after myocardial infarction, N. Engl. J. Med. 381 (2019) 2497–2505.

149. S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, for the LoDoCo2 Trial Investigators, et al., Colchicine in patients with chronic coronary disease, N. Engl. J. Med. 383 (2020) 1838–1847.

150. K. Nelson, V. Fuster, P.M. Ridker, Low-dose colchicine for secondary prevention of coronary artery disease: JACC review topic of the week, J. Am. Coll. Cardiol. 82 (2023) 648–660.

151. T. Opstal, A. Fiolet, A. van Broekhoven, A. Mosterd, J.W. Eikelboom, S.M. Nidorf, P.L. Thompson, M. Duyvendak, J.W.M. van Eck, et al., Colchicine in patients with chronic coronary disease in relation to prior acute coronary syndrome, J. Am. Coll. Cardiol. 78 (2021) 859–866.