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Pathogenesis, Etiology, Epidemiology, Pathophysiology, Complications And Pharmacotherapy Of Atherosclerosis

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Abstract: One of the biggest risk factors that has been identified as influencing the frequency and severity of coronary heart disease is hyperlipidemia. The main causes of death are hyperlipidemia, atherosclerosis, coronary heart disease, and stroke. Elevations in low density lipoprotein and serum total cholesterol have been identified as the main risk factors for cardiovascular disease. A disorder known as hyperlipidemia occurs when the blood contains excessively high amounts of lipids, or fatty molecules. Drugs that lower cholesterol are often used as preventative measures to stop atherosclerosis-related problems. The most prevalent preventable factor contributing to atherosclerotic cardiovascular disease is hyperlipidemia. The idea that low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol are inversely correlated with the onset of a major adverse cardiovascular event is a result of our growing understanding of controlling hyperlipidemia. Excess lipid, or excess body fat, is a defining feature of atherosclerosis, a chronic, complicated, multifactorial, and morbid disease that negatively affects health. The prevalence of hyperlipidemia has significantly increased in the last few years, making it a global health concern. The etiology of hyperlipidemia is complicated and includes interactions between heredity, the environment, and hormones. The development of atherosclerotic plaques is the primary cause of hyperlipidemia. The various problems linked to hyperlipidemia are obesity, hypertriglyceridemia, hypertension, type-2 diabetes mellitus, hypothyroidism, fatty liver disease, osteoarthritis, respiratory problems, stroke, cancer, dementia, depression, gynaecologic problems, social-psychological problems, chronic kidney disease etc. There are various approaches for the management and treatment of hyperlipidemia, that is lifestyle modifications, anti-hyperlipidemia medicines, anti- P selectin therapy, Angiopoietin Like Targeting Agents and photodynamic therapy. Lifestyle modification is still the backbone of managing obesity. Anti-hyperlipidemic medicines are used to reduce cholesterol levels by lifestyle modifications.

Index Terms **-** Hyperlipidemia, Thrombosis, Lipid indices, Castelli index, Theranostics, Atherosclerotic plaques.

I. INTRODUCTION

Atherosclerosis is a disease which affects cerebral and corneal arteries. It is mainly due to accumulation of lipids and triglycerides plagues in blood vessels. It could be diagnosed by angiography. Heart disorders are still the main reason of death and morbidity rates throughout the world (Roth, G. A., *et al*., 2020). Worldwide, the main reason of death and morbidity for both sexes is still heart disorders, the primary sign of hyperlipidemia (Ralapanawa, U. and Sivakanesan, R., 2021). However, when atherosclerosis progresses, other heart disease also develops (Wilson, H. M., 2022). Furthermore, it's important to remember that endovascular treatments are crucial for treating atherosclerotic disorders; nevertheless, their efficacy is limited

by restenosis, which also increases the need for reintervention (Jakubiak, G. K., *et al.,* 2021). Lipids have also been implicated as important actors and regulators of these processes (Li, L., *et al.,* 2022). In clinical practice, the profile of lipid has long been regarded as a crucial instrument for evaluating the cardiovascular disease. However, in comparison to conventional single lipid measures, several non-traditional lipids and indicators have also been developed, which demonstrate an even greater predictive effect of cardiovascular diseases (Fernandez, M. J. C., *et al*., 2019).

When lipid levels in the blood are higher than usual, it is referred to as hyperlipidemia and can result in serious consequences (Nirosha, K., *et al.,* 2014). The development of atherosclerosis and its associated conditions, including peripheral vascular disease, cerebral vascular disease, brain strokes, and cardiovascular disease, are typically linked to these difficulties (Shattat, G. F., 2015). These lipids, particularly cholesterol, are deposited in the walls of the arteries, restricting them and preventing enough blood flow through them (Bahmani, M., *et al.*, 2015) and cause hyperlipidemia.

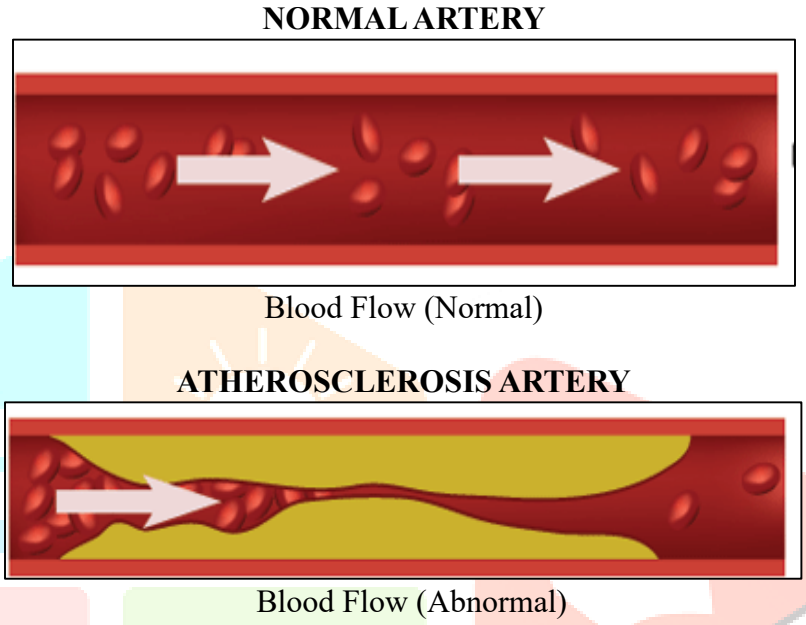

Figure-(1): Effect of elevated level of lipid on blood flow

Proteins and lipids combine to form macromolecules called lipoproteins. Apo lipoproteins are other name of several proteins. Amphiphilic proteins, sometimes referred to as apo lipoproteins, bind to plasma and lipids (Carpentier, Y. and Sobotka, L., 2008). Insulin activity rises following a meal heavy in lipids and carbohydrates. When the CM atoms pick up cholesteryl esters, these fragments also undergo alignment modifications. The Cholesteryl Ester Transfer Protein facilitates exchange of cholesteryl esters from lipoproteins that contain cholesterol, which causes the change (Rani, R.R., Banu, Z. and Rahman, A., 2024).

Hyperlipidemia is classified as primary or secondary based on its cause. Primary hyperlipidemia is often caused by a blend of genetic and environmental aspects, although it could also be produced by a single inherited genetic problem. Secondary hyperlipidemia can result from a number of underlying conditions, including diabetes, hypothyroidism, and too much alcohol. Numerous licensed medications are available to treat hyperlipidemia. However, the effectiveness and tolerance of these drugs vary from person to person, and certain individuals may experience unexpected adverse effects (Anees, S., *et al*., 2024). The main reason of death in the world is heart disorders, accounting for over 56% of cases and resulting in around 4.4 million fatalities annually. In 2019, heart disease was the biggest basis of death worldwide, accounting for about 17.9 million fatalities. Cardiovascular diseases now account for approximately 28% of the deaths in India, a significant increase over previous decades. The considerably higher prevalence of ischemic heart disease in South India compared with the northern regions is indicative of regional variations in the illness's burden (Rani, R.R., Banu, Z. and Rahman, A., 2024).

The majority of non-communicable diseases that cause death (17.9 million annually) are caused by cardiovascular health issues, which are followed by cancer, respiratory disorders, etc (WHO. Noncommunicable diseases, cited Sep 16, 2022). The underlying pathophysiology and progression of almost all heart disorders are atherosclerotic lesions, various heart disease, that eventually ends in myocardial infarction and stroke. High density lipoprotein is a key goal for the management and prevention of

cardiovascular disorders and is included in the criteria for diagnosis for metabolic syndrome. Each phase of the atherosclerosis process depends heavily on lipids.

II. PATHOGENESIS OF DYSLIPIDEMIA

The pathophysiology of atherosclerosis includes interactions between endothelial dysfunction, oxidative stress, inflammatory pathways, hereditary predisposition, and lipid metabolism imbalance. Vascular smooth muscle cells, inflammatory cells along with endothelial cells, all play an important part in the onset and course of disease.

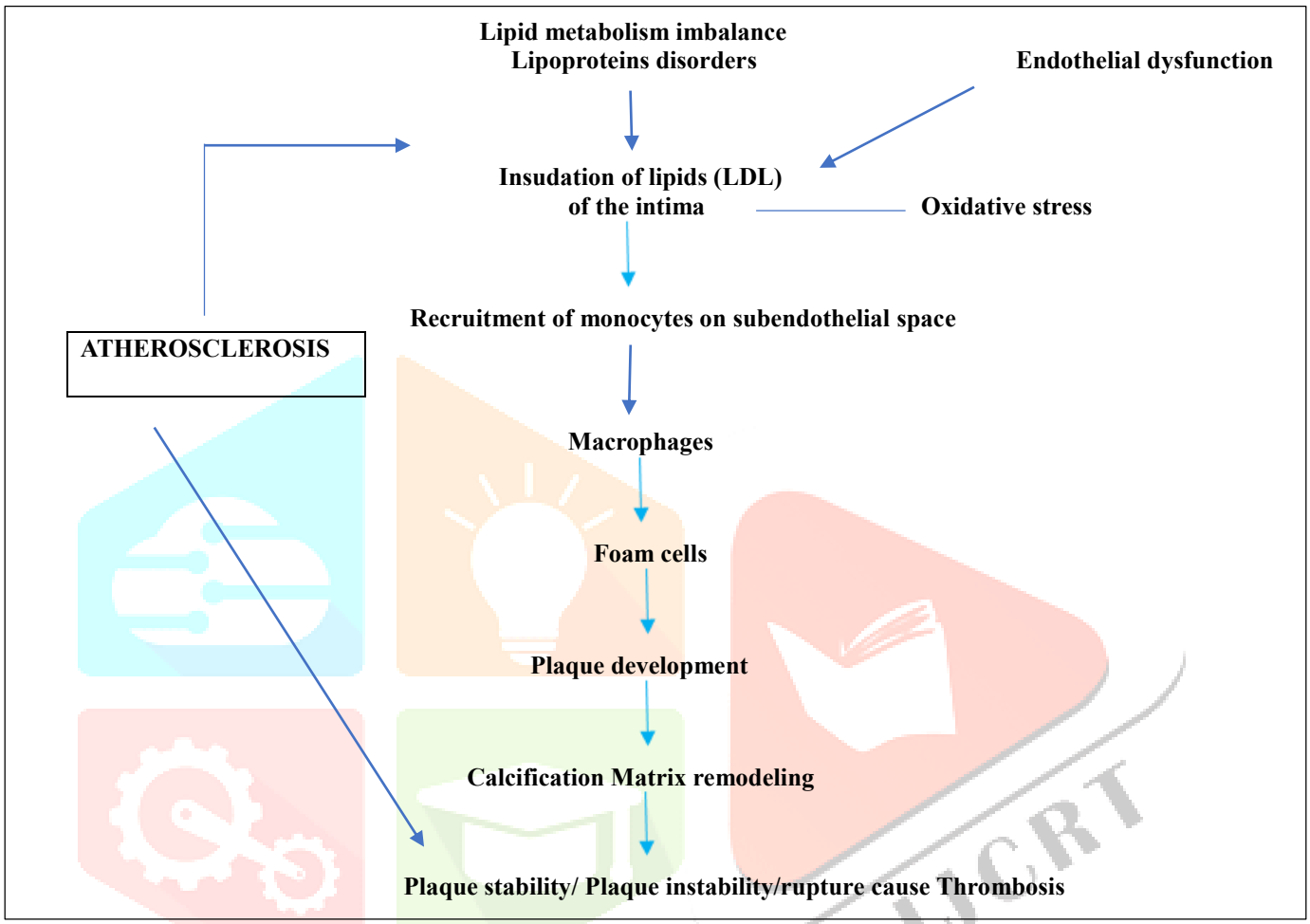

Figure-(2): Pathogenesis of atherosclerosis

III. EPIDEMIOLOGY AND ETIOLOGY

Hyperlipidemia is mostly asymptomatic; it is difficult to regulate its exact incidence. It is believed that plaque is the primary cause of heart diseases. Stroke comes in fifth place globally, but ischemic heart disease is the main cause of mortality. According to estimates, heart disease claims the lives of 610,000 Americans annually. A single death among four. More than 370,000 people die due to heart disease each year. Around 735,000 Americans goes through from heart attack each year. Amongst them, 525,000 people suffer from initial attack and 210,000 patients suffer from recurring attacks. Rupture of plaque is said to be the cause of 75% of acute myocardial infarctions, with the largest frequency occurring in males over 45 and in women after the age of 50. Although it is lost after menopause, the preventive function of female sex hormones is believed to be the cause of men's greater risk of atherosclerosis compared to women (Pahwa, R. and Jialal, I., 2023). Nearly 795,000 people in the US are reportedly affected by stroke, which claims the lives of approximately 140,323 people annually. The most prevalent kind of stroke, ischemic stroke, is brought on by cardiovascular disorders. Atherosclerosis may be exacerbated by its impact on inflammation and low-density lipoprotein particles (Pahwa, R. and Jialal, I., 2023).

Atherosclerotic cardiovascular disease has a complicated etiology. The most common parameters include diabetes, smoking cigarettes, aged (male over 45, female over 55), male gender, hypercholesterolemia, and having a history of diabetes in the family (male relative under 55, female under 65). Sedentary lifestyles, obesity, diets high in trans and saturated fats, and some genetic disorders are other risk factors. Pharmaceutical

treatments that increase high density lipoprotein cholesterol have had unfavourable results, which raises concerns about high density lipoprotein role in atherosclerosis cardiovascular disease even while low levels of high-density lipoprotein cholesterol are believed to constitute risk factors.

IV. PATHOPHYSIOLOGY

High Low- density lipoprotein is one of the most common risk parameters for atherosclerosis. High blood lipid or fat concentrations is the easiest method to demonstrate it. Various factors such as tobacco use, damage of endothelial, elevated cholesterol levels, inflammation, rupture of plaque, and high blood pressure, can lead to coronary artery disease. Atherosclerosis frequently goes undetected if plaque stenosis reaches 70 to 80% of the vessel's diameter. This process can lead to lipid accumulation in the innermost portion of the endothelial wall, which raises inflammation in the immediate vicinity of the defective area. Majority of individuals have polygenic hyperlipidemia due to person's consumption of saturated fat, cholesterol, and (central) obesity. Atherosclerotic disease can also be brought on by high levels of "apo B-100" lipoproteins, even in individuals who do not have any other risk factors. Numerous environmental and genetic factors often contribute to an individual's risk of high levels of cholesterol and heart disease. Atherosclerosis is the accumulation of fatty acids, debris, along with calcification within the main arteries. Endothelium activation starts this process, which is followed by a series of events that could point to vascular constriction and the start of the inflammatory pathways that cause atheroma plaque to form.

4.1. INITIATION OF ATHEROSCLEROSIS

The vascular endothelium is composed of endothelial cells that confronts the interior side of all the blood arteries, serves as the first line of protection for substances, cells travelling through the circulation (Reitsma, S., *et al*., 2007). Along with collagen and elastic fibres, the endothelium, a single endothelial cell layer which lines the vessel wall of large vessels, makes up the luminal layer of the vessels, sometimes referred to as intima. Endothelial cells are in close contact with the tunica medium, which is composed of smooth muscle cells from the vascular system and collagenous and elastic cells. This layer is enveloped by the tunica adventitia, that is consists of a matrix of connective cells. In the end, post-capillary venules are completely devoid of adventitia and media, consisting solely of ECs and a basement membrane (Rhodin, J.A., 1968). It appears that vessel segments with low wall shear stress or significantly oscillatory wall shear stress are more likely to develop atherosclerosis (Roger, V. L., *et al*., 2001; Targonski, P., 2001). Changes in wall shear stress can promote the movement and growth of vascular smooth muscles and mononuclear cells and have a direct impact on the shape and activity of the vascular endothelium (Boyum, A., 1968).

4.2. ENDOTHELIAL LAYER DYSFUNCTION

Endothelial dysfunction is promoted by hemodynamic pressures, which constitute an immediate threat for atherogenesis. Where laminar flow is disrupted by separation of flow, recirculariza tion, or reconnecting, lesion-prone zones are most commonly observed. The temporal and geographical gradients created by such turbulent flow results in greater oscillating index and a smaller shear stress (Chiu, J.J. and Chien, S., 2011).
Additional explanations for endothelial dysfunction include a reduction in nitric oxide bioavailability (Landmesser, U., Hornig, B. and Drexler, H., 2000). Nitric oxide is generated by L-arginine in endothelial cells via a process driven by eNOS, which then travels through cell membranes and enters the tissue of smooth muscle of the artery wall. Among other things, nitric oxide plays a part in platelet aggregation reduction, oxidation of tissue and inflammatory disorders, thrombogenic factor activation, and growth of cell, movement and growth (Cooke, J.P. and Tsao, P.S., 1994; Libby, P., 2001; Marx, N., *et al*., 1999; Chen, J.Y., *et al*., 2018) (Figure 3).

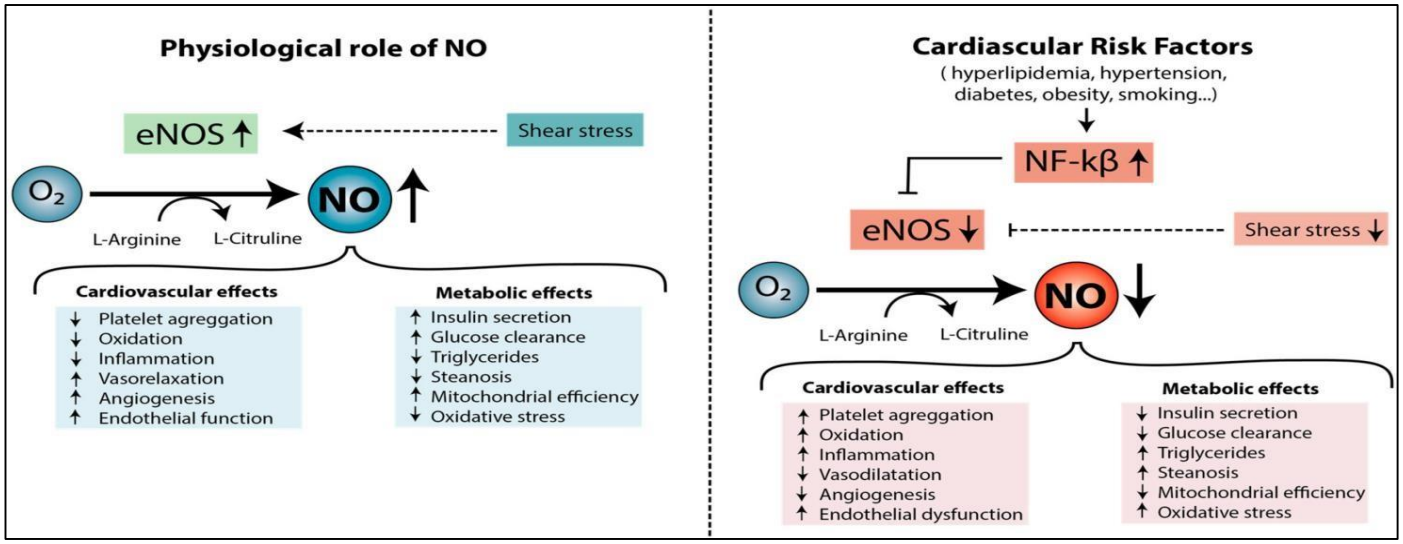

Figure (3): Physiological role of nitric oxide and cardiovascular risk factors

Nitric oxygen, which regulates cardiovascular metabolism, is compromised when cardiovascular risk factors are present. The transformation of L-arginine to nitric oxide is catalysed by e-nitric oxide. Nitric oxide is crucial molecule that slows the growth of atherosclerosis while enhancing the function of endothelial cells, angiogenesis, relaxation of vessels, production of insulin, glucose elimination, and mitochondrial performance. Conversely, it reduces oxidative stress, inflammation, stenosis, as well as plasma lipid levels. Risk parameters of heart disease inhibit e-nitric oxide function when NF-kβ is triggered, lowering nitric oxide and promoting the development of atherosclerosis (Benslaiman, S. B., *et al*., 2022).

4.3. FORMATION OF FOAM CELLS/ THROMBUS

Plasma low-density lipoprotein accumulation promotes trans endothelial penetration of circulatory low-density lipoproteins to the intima. Low-density lipoprotein trans endothelial transport is now known to be significantly influenced by transcytosis (Jang, E., *et al*., 2020; Zhang, X., *et al*., 2018) despite the widely held belief that low-density lipoproteins diffuse or paracellularly penetrate the endothelium (Michel, C.C. and Curry, F. E., 1999; Rippe, B., *et al*., 1994; Rippe, B., *et al*., 2002; Pappenheimer, J.R., *et al*., 1951).
Endothelial progression, also called as endothelium type I activation, initiates when inflammatory chemicals result in a modification in permeability, microvascular tone, or leukocyte diapedesis (Liao, J.K., 2013; Pober, J.S. and Sessa, W. C., 2007).

The fibrous crown and necrotic core are characteristics of advanced atherosclerosis (Lusis, A.J., 2000), and the atheroma lesion relapse is not expected to happen at this point (Fisher, E.A., *et al*., 2012; Puri, R., *et al*., 2013). Outward vascular remodelling initially avoids lumen constriction in order to maintain an ordinary lumen and recover the pattern of shear stress. On the other hand, this condition worsens plaque formation. The lesion becomes more prone to rupture when the upper portions of the plaques at preserved lumen regions experience greater tensile stress (Slager, C.J., *et al*., 2005). Plaques with a high necrosis core, a narrow fibrous crown, along with high inflammation are considered vulnerable because of their exposure to the atherogenic environment (Stefanadis, C., *et* al., 2017; Cuadrado, I., *et al*., 2016). The vulnerability of the plaque is associated with the thickness of the fibrous cap, which separates the thrombogenic necrotic core from the platelets in circulation and factors that promote coagulation (Badimon, L., Padro, T. and Vilahur, G., 2012). Since vascular smooth muscle cell death results in a decrease in extracellular matrix synthesis and a rise in secreted matrix metalloproteinases, the fibrous cap weakens (Sodhi, N. and Brown, D.L., 2019). Inflammation contributes to the formation of plaque from the time of start to its rupture. It is significant in this last phase because this encourages the uncertainty of the fibrous cap (Libby, P., 2002).

When the plaque breaks, exposing the subendothelial region to blood, a process of coagulation is started to protect the plaque (Vergallo, R. and Crea, F., 2020). Platelets initially adhere to and stimulate the subendothelial collagen to initiate wound healing, following which they are drawn to and collected in the region (Yun, S.H., *et al*., 2016). More specifically, interaction among tissue factors causes production of

thrombin, an essential step in the synthesis of fibrin (Osaki, T. and Ichinose, A., 2014). Fibrin forms connections of threads of fibrin which cover the lesion in conjunction with platelets to produce a solid, well-organized structure. This formation is known as thrombus. Moreover, certain antibodies that ox-low density lipoprotein connects to may create immunological complexes that inflame macrophages and dendritic cells. These immune complexes mainly activate cells, produce inflammatory cytokines, and produce foam cells (Lopes-Virella, M.F. and Virella, G., 2013).

V. DIAGNOSIS, TREATMENT AND EVALUATION

A complete series of parameters should be compiled by physicians while evaluating a patient for hyperlipidemia. Certain factors such as PCSK9 gain of function mutations, lipoproteinemia, hereditary defective apo B-100, familial high cholesterol levels, and familial mixed elevated lipid levels must also be considered. Several other disease processes must also be considered when diagnosing hyperlipidemia in a patient (Vodnala, D., et al., 2012). A complete history, physical examination, and extensive blood conditions should be conducted in order to reduce the differential and arrive at the correct diagnosis. Although hyperlipidemia is usually quite treatable, it is frequently a lifelong disease process. Untreated hyperlipidemia, on the other hand, is a progressive condition that frequently results in serious underlying vascular disease processes that can be lethal. Early adulthood contacts to high lipid levels enhance a person's risk of cardiovascular issues later in life (Vallejo-Vaz, A.J., *et al*., 2017). Using data from the "West of Scotland Coronary Prevention Study," which was followed up on for 20 years, the investigators found that people who took statin therapy for five years had better life expectancy and a statistically decrease in heart issues over that time. This information corroborates many additional research that show that taking statin medicine as prescribed significantly lowers the risk of cardiovascular disease, and that a proactive treatment strategy was used (Ford, I., *et al*., 2016). In patients who have not yet been diagnosed with cardiovascular disease, only treatments for high levels of low-density lipoproteins cholesterol are being demonstrated to be clinically helpful in reducing risk. There are no proven therapeutic benefits to treating hypertriglyceridemia or low high-density lipoprotein cholesterol.

There are conflicting recommendations on the age at which physicians must begin screening and the frequency of hyperlipidemia screenings. Generally, a person must have a routine lipid check-up when he turns 35 (if he has no other heart disease risk factors) or 25 (if he has other cardiac risk factors). Additionally, it is recommended that women begin routine cholesterol check-up at age 45 (if they do not have any other heart disease risk factors) or between the ages of 30 and 35 (if they do) (Fredrickson, D.S., 1971). For nine to twelve hours, you must only consume water and nothing else to avoid distorting the lipid panel's results, particularly the triglyceride levels.

VI. COMPLICATIONS

All forms of vascular disease can eventually prove to be lethal. The side effects of statin drugs include myopathy, renal damage, arthralgia, aches in the extremities, nausea, myalgia, elevated liver enzymes/hepatotoxicity, diarrhoea, and rhabdomyolysis. Muscle-related sensitivity may develop in as many as 5–20% of statin medication users (Nissen, S.E., *et al.,* 2016). Aerobic exercise enhances good cholesterol protein levels, that have been shown to have an anti-atherogenic effect. Incorporating 10 minutes of physical activity to each day is thought to increase high-density lipoprotein concentration by 1.4 mg/dl, and a suitable training program has been observed to improve high-density lipoprotein cholesterol by an average of 4.6%. (Franklin, B.A., *et al*., 2020). Both aerobic and anaerobic exercises have the same potential to raise blood cholesterol levels (Alvarez, C., *et al*., 2019). Training with resistance (anaerobic activity) for one hour a week may enhance one's lipid profile and is a suitable indication to avoid overdoing physical exertion and to maintain optimal health (Bakker, E. A., *et al*., 2018). Additionally, the person has to be conscious of the possible consequences of skipping prescription and other treatment options available to them (Marcus, F. H. and Bordoni, B., 2023). The doctor usually needs to work with nurses to get vital signs, ask about the patient's history, and other tasks that are essential to providing quality patient care. The primary care physician usually uses diet, exercise, and/or medication to treat the illness after diagnosis. For the best care, the patient's other doctors must be informed of this evaluation and therapy plan. Additionally, it entails the prescribing physician and, if necessary, the pharmacist communicating with the patient of the adverse effects of the medication. Additionally, the pharmacist can reiterate any potential adverse reactions or interactions from the drugs that the doctor has given. A nutritionist or dietitian can often be consulted by the patient if nutritional education is required. To closely monitor the disease's course, the patient should be checked annually or more frequently (Marcus, F. H. and Bordoni, B., 2023).

VII. CHARACTERIZATION OF LIPOPROTEIN

Specialized biochemical assemblages known as lipoproteins are necessary for the bloodstream to carry lipids, including cholesterol and triglycerides. Lipids are unable to pass easily through the plasma due to their hydrophobic nature. Lipoproteins fight this by enclosing triglycerides in a core that is encased in a shell made of cholesterol, phospholipids, and proteins known as apolipoproteins (Rani, R.R., Banu, Z. and Rahman, A., 2024).

Types	Cholesterol levels	Bad Cholesterol	Triglyceride	Abnormality Lipoprotein	Major causes	Other causes
I	High	Low/ Moderate	Elevated	High chylomicrons	Deficiency of Apolipoprotein	Systemic lupus
II a	High	High	Normal	High LDL	Family history	Hypothyroidism
II b	High	High	High	High LDL and VLDL	Family history	Diabetes, anorexia
III	High	Low/ Moderate	High	High chylomicron remnants/ IDL	Type II familial hyperlipoprotein emia	Hypothyroidism
IV	High	Moderate	High	High VLDL	Hypertriglyceridemia	Kidney diseases
V	High	Moderate	High	High chylomicrons	Hypertriglyceridemia	Diuretics, Alcohol

Table 1: Classification of hyperlipidemia (According to Frederickson) (Keefe Jr, J.H.O., Cordain, L., Harris, W.H., *et al*., 2004)
HDL: High- density lipoprotein; LDL: Low- density lipoprotein; VLDL: Very low-density lipoproteins; IDL: Intermediate density lipoprotein

VIII. CORRELATION OF HYPERLIPIDEMIA WITH OTHER DISEASES

9.1. Diabetes

The dyslipidemia is characterized by high triglycerides, cholesterol levels (Wu, L. and Parhofer, K. G., 2014). 60% to 70% of diabetes patients exhibit at least one lipid problem, while not all patients exhibit all symptoms. One significant connection between cardiovascular disease and diabetes is dyslipidemia. The distinctive lipid alterations are thought to be a reflection of resistance to insulin rather than hyperglycaemia because they are observed among individuals with metabolic syndrome as well as those with overt diabetes. Additionally, it is well recognized that while dyslipidemia is improved by proper glucose management, it is not completely eradicated. Hypertriglyceridemia is caused by the overproduction of intestinal and hepatic lipoproteins as a result of inflammation and the body's overabundance of energy-rich substrates (Adiels, M., *et al*., 2008). It has been acknowledged in recent years that lipid alterations may both induce and result from poor glucose metabolism. In the situation, low high-density lipoprotein cholesterol and hypertriglyceridemia are significant. Increased triglyceride levels cause free fatty acid levels to rise, which can cause βeta-cell malfunction along with insulin resistance (Briaud, I., *et al*., 2001). Although the precise mechanisms are still unclear, it appears that high levels of fatty acids may interfere with or alter the cascade that connects insulin receptors to glucose transporters, which hinders the β-cell's ability to function normally (Rachek, L.I., 2014). Free fatty acids also play a significant role in regulating inflammation. Consequently, subclinical inflammation brought on by hypertriglyceridemia may result in insulin resistance and β-cell dysfunction.

According to more recent research, high-density lipoprotein may also have a direct impact on the metabolism of glucose (Drew, B.G., *et al*., 2012). Higher high-density lipoprotein cholesterol concentrations were linked to lower levels of hyperglycaemia (Barter, P.J., *et al*., 2011). Additionally, recombinant HDL infusion has been shown to enhance glucose metabolism in patients with diabetes (Drew, B.G., *et al.*, 2012). Numerous investigations have since attempted to clarify the underlying pathophysiology, and a number of mechanisms have been found (Lehti, M., *et al*., 2013; Mortensen, S.P. and Boushel, R., 2013). It is thought that HDL reduces micro-inflammation by causing reverse cholesterol transfer and altering the intracellular lipid environment. Moreover, HDL's direct anti-inflammatory qualities might potentially be involved.

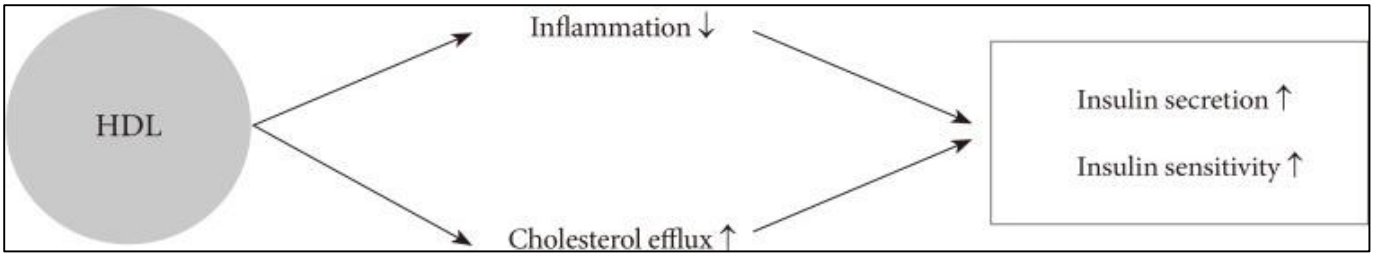

Figure (4): HDL and insulin correlation

There are several possible connections between glucose metabolism and high-density lipoprotein. At least some subtypes of high-density lipoprotein have direct anti-inflammatory effects. Additionally, high-density lipoprotein mediates the release of cholesterol from numerous tissues and are the main player in reverse cholesterol transport. This could alter the microenvironment in a way that improves insulin secretion and sensitivity.

Recently, it was demonstrated in a mouse model that apolipoprotein A1 overexpression enhances glucose metabolism, leads to a larger lean body mass, and increases the production of mitochondrial adenosine triphosphate synthase, whereas apoA1 knockout produces a clinical picture mimicking metabolic syndrome (Lehti, M., *et al*., 2013). It's interesting to note that apoA1 overexpression may also shield against diet-induced obesity in the same model. Despite the significant differences in lipoprotein metabolism between humans and rodents, these findings may potentially serve to clarify how human HDL and glucose metabolism interact.

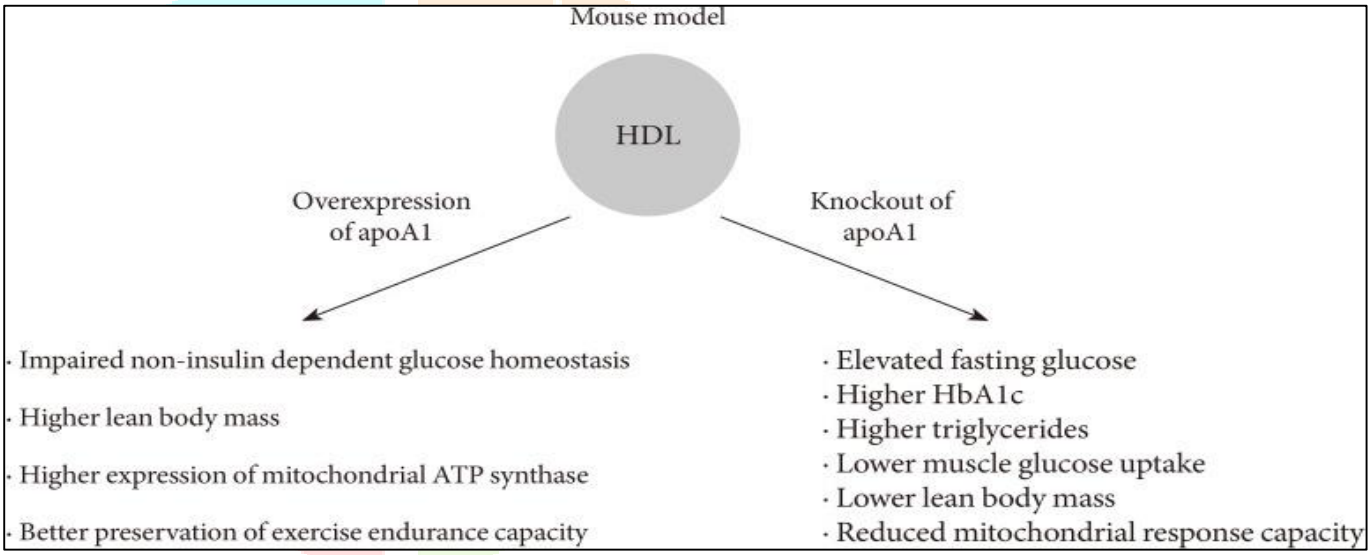

Figure 5: Animal mouse model (Lehti, M., *et al*., 2013).

9.2. Cardiovascular disease

Due to their extensive impact on rates of sickness and mortality, cardiovascular diseases are a serious global health issue that requires attention. The World Health Organization reports that heart disorder leads to over 17.9 million deaths per year, making it the major cause of mortality worldwide (Zhao, M., *et al*., 2015). Hereditary, ecological, and psychological variables interact intricately in the complicated etiology of cardiovascular diseases. Dyslipidemia is one of these variables that is essential to the growth of cardiovascular diseases. Given the global significance of cardiovascular diseases, a comprehensive examination is necessary to completely comprehend their enormous reach. Recent research indicates that the prevalence of cardiovascular diseases is rising, posing a serious public health concern in numerous groups and geographical areas. As healthcare systems around the world grapple with the rising costs associated with the early detection, treatment, and management of cardiovascular diseases, the economic effects of these disorders are equally significant (Zhao, M., *et al*., 2015). The numbers demonstrate the urgent need for a comprehensive understanding of the risk factors associated with cardiovascular diseases, with a particular emphasis on lipid disorders. The aging of the population, urbanization, and changes in lifestyle are all strongly linked to the rise in cardiovascular diseases. The burden of cardiovascular problems is made worse in low- and middle-income countries by the transition from infectious to non-infectious diseases. The transition is fuelled by dietary

changes, sedentary lifestyles, and a rise in obesity. All of these elements have a part in the global impact of lipid-related conditions and, consequently, cardiovascular diseases. The progression of cardiovascular diseases, particularly atherosclerosis, the main pathological process causing the majority of cardiovascular events, is significantly correlated with lipid issues. These abnormalities are collectively referred to as dyslipidemia. The onset and progression of cardiovascular diseases are intimately linked to the growth of atherosclerotic lesions in the artery walls, which are made possible by these lipid abnormalities (John Mancini, M.D., *et al*., 2011). The link between dyslipidemia and poor cardiovascular outcomes has been amply demonstrated by several epidemiological studies and clinical trials. Beginning in 1948, the well-known Framingham Heart Study played a significant role in elucidating the connection between high cholesterol and heart disease. Additional research on the efficacy of treatments that reduce lipid levels in avoiding cardiovascular events has been made possible by studies like the Scandinavian Simvastatin Survival Study and the Lipid Research Clinics Coronary Primary Prevention Trial (John Mancini, M.D., *et al*., 2011). Accumulation of lipoproteins that encourage the development of atherosclerosis in the inner layer of the arteries explains the connection between these two factors. This results in a number of inflammatory responses and modifications to the blood vessel structure (John Mancini, M.D., *et al*., 2011). To fully understand the complexities of cardiovascular risk, it is imperative to understand the complex dynamics of lipid disorders. This large-scale study provides a thorough summary of contemporary perspectives on lipid disorders and their important effects on cardiovascular health. Our goal is to examine a large body of research in order to comprehend the intricate relationships between atherosclerosis and cardiovascular diseases. We shall concentrate on the environmental, genetic, and molecular factors that contribute to these diseases (Almeida, J.T., *et al*., 2020). Ongoing developments in biomarkers and imaging methods, coupled with the evolving landscape of cardiovascular health, present opportunities for more accurate risk assessment (Bianconi, V., Banach, M. and Pirro, M., 2021). Personalized treatment techniques could be made possible by integrating genetic and molecular analysis into clinical practice. However, in order to truly improve patient outcomes, it is imperative to evaluate the existing knowledge gaps in detail and use these innovations appropriately.

9.3. Hyperthyroidism

The production and metabolism of hepatic fatty acids and cholesterol have long been known to be significantly impacted by thyroid hormones. In fact, non-alcoholic fatty liver disease, high triglyceride along with cholesterol have been linked to hypothyroidism. These actions are mediated by thyroid hormone through autophagy, transcription, and post-translational processes. Thyroid hormone mimetics and/or analogues may be helpful in treating liver-related metabolic illnesses such non-alcoholic fatty liver disease and hypercholesterolemia. Thyroid hormones play an important role in controlling overall growth in mammals. Numerous metabolic processes that are controlled by thyroid hormones have to do with the anabolism or catabolism of macromolecules like proteins, lipids, and carbohydrates that impact energy homeostasis under various dietary circumstances. In fact, the direct effect of thyroid hormone over production and metabolism of fatty acids and cholesterol have long been recognized. While thyroid hormone treatment lowers the levels of cholesterol in the blood, hypothyroidism may be linked to elevated serum levels of these cholesterols (Duntas, L.H., 2002). Similarly, hypothyroidism can result in elevated serum triglyceride levels, while hyperthyroidism causes the opposite effect (Duntas, L.H., 2002). In the past, high-dose has been used to treat hypercholesterolemia and encourage weight loss in obese patients (Krotkiewski, M., 2000). Despite positive reports, significant cardiac issues and lean body mass loss prevented T3 from being developed further as a treatment (Krotkiewski, M., 2000). However, many of the proteins, carriers, transport proteins, and cell-signalling protein molecules associated with liver lipid homeostasis can also be regulated by metabolic concentration, cell energy status, and post-translational modifications that occur downstream of thyroid hormone's transcriptional effects (Brijesh, K. S., et al., 2016a, Brijesh, K. S., et al., 2013b).

9.4. Alcoholism

The most common form of liver disorder with a high global death rate is alcoholic liver disease. Alcoholic liver disease begins with simple liver steatosis and develops into cirrhosis, fibrosis, and alcoholic steatohepatitis. Later stages of alcoholic liver disease are related with the severity of steatosis of the liver. About two billion individuals drink alcohol worldwide, and alcohol misuse is a major contributor to liver-related disease and death (Asrani, S. K., *et al*., 2019). Despite alcoholic liver disease's significant negative effects on health and the economy, there are currently no approved treatments to stop or reverse the disease in patients. Steatosis, or excess fat buildup, is the most common and early liver reaction to alcohol. When liver fat surpasses 5% of weight of liver due to alcohol consumption, alcoholic fatty liver is identified. Steatosis, which is generally regarded as a low harmful stage as compared to advanced stages of liver disease, develops in almost

all alcohol users (Edmondson, H. A., *et al.,* 1967). However, the onset of later phases of alcoholic liver disease, which are caused by alcohol's harmful consequence on liver metabolism of lipid, is closely linked to the severity of this disorder. In contrast, although the severity of alcoholic liver disease is strongly correlated with alcohol consumption, most consumers do not have severe liver disease from alcohol consumption alone (Lazo, M., and Mitchell, M.C., 2016). The majority of evidence suggests that hepatic lipid dysregulation occur due to metabolism of alcohol itself, with the liver being the primary organ in charge of converting consumed alcohol into the harmful metabolite acetaldehyde (Zakhari, S., 2006). Alcohol has numerous effects on liver lipid homeostasis after it has been digested, which encourages steatosis.

9.5. Liver disorder

An important location for lipid and energy metabolism is the liver. People who accumulate too much fat in their livers are more likely to develop cirrhosis, fibrosis, and hepatocellular carcinoma later in life. As has been shown for harmful, viral, and cholestatic insults, steatosis is also a significant comorbidity that exacerbates liver damage and disease development in diseases of different causes. When steatosis is absent, less is known about how much lipids and lipid metabolism affect liver disorders. There are already indications that lipid buildup is not a major cause of organ damage. Lipid droplets are, in fact, extremely sophisticated organelles that enable cells to manage the storage and release of lipids (Thiele, C. and Spandl, J. (2008) Furthermore, it has been suggested that lipids are kept safe by being compartmentalized in droplets (Kanji, Y., *et al.,* 2007, Neuschwander-Tetri, B.A., 2010, Ni-Huiping, S., *et al*., 2010). However, the primary process of lipid-mediated liver injury is the movement of lipids into and out of these droplets, which transforms inactive molecules into potentially harmful mediators. The fact that lipids may have an impact on liver cell types other than hepatocytes is a second often disregarded point. Large quantities of lipids are deposited in droplets within hepatic stellate cells, formerly known as hepatic "lipocytes." It is possible that lipids in liver illnesses could target hepatic stellate cells or other nonparenchymal cell types. What kinds of lipids cause liver illness and injury is a third crucial factor to take into account.

Certain dietary lipids, like cholesterol or trans-fats, may be more important for the development of diseases like liver damage, inflammation, and fibrosis, even if total caloric and fat intake is a main factor for progression of weight gain and liver steatosis (Mari, M., Caballero, F. and Colell, A., 2006, Kohli, R., Kirby, M. and Xanthakos, S.A., 2010).

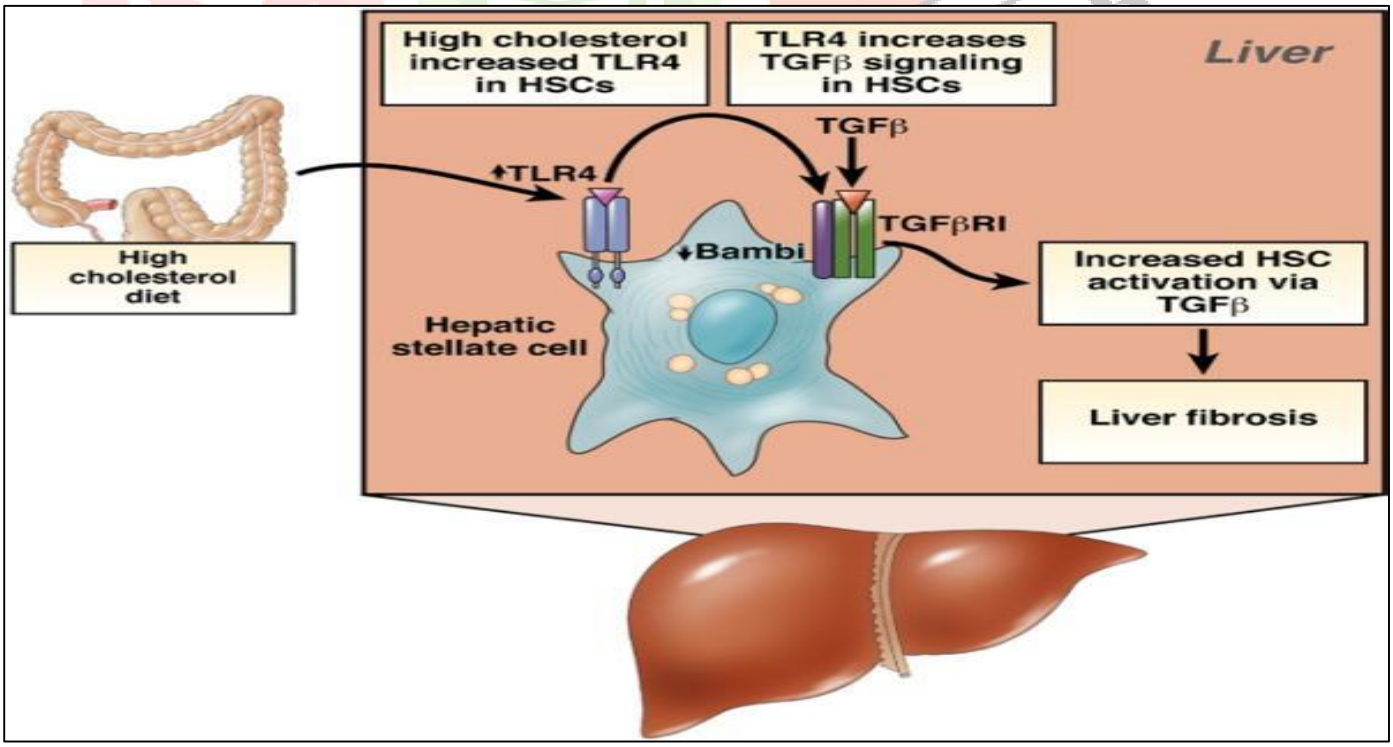

Figure (6): Interaction of lipid and liver cells

IX. PHARMACOTHERAPY

Classification of drugs (Maheshwari, K.K., 2012)

1.Bile acid binding resins or anion exchange resins (Interfere with intestinal absorption of bile salts/ cholesterol): Cholestyramine, Colestipol, B- sitosterol, Colesevelam, Divistyramine
2. Fibrate (Fibric acid= Isobutyric acid) derivatives: Bezafibrate, Clofibrate, Gemfibrozil, Fenofibrate, Coprofibrate
3. Inhibits VLDL production and lipolysis: Nicotinic acid or niacin
4. HMG-CoA reductase inhibitors or fungal metabolites or statins: Atorvastatin, Fluvastatin, Mevastatin, Rosuvastatin, Cerivastatin, Lovastatin, Pravastatin, Simvastatin
5. Antioxidant: Probucol
6. Dietary cholesterol Inhibitors: Ezetimibe
7. Cholesteryl ester transfer protein inhibitors: JTT-705, Torcetrapib
8. Miscellaneous agents: Acipimox, Glycocholic acid, Taurocholic acid, Estrogens, Gugulipid, Metformin, Pindolol, Sucrose Polymers, Eicosapentaenoic acid, Fish Oil, Lipin, Neomycin, Propranolol
9. Renin–Angiotensin System (RAS) Inhibitors: Captopril, enalapril, perindopril (Aprotosoaie, A.C., Costache, A. D. and Costache, I. I., 2022)
10. Monoclonal antibody: Ziltivekimab (Aprotosoaie, A.C., Costache, A.D. and Costache, I.I., 2022)

7.1. STATINS

These are generally given drugs for the therapeutic supervision of cardiovascular risk and as first-line therapy for atherosclerosis. They are effective in avoiding cardiovascular disease at both the initial and later phases. They have several non-lipid-related pleiotropic effects in addition to their potent LDL-lowering effects. These include enhancing nitric oxide (NO) accessibility, decreasing endothelial dysfunction, exhibiting antioxidant, immunomodulatory, and anti-inflammatory qualities, improving plaques at the heart, and averting cardiac hypertrophy (Davignon, J., 2004).

A. Mechanism of Action: Statins block HMG-CoA reductase, the main enzyme that is accountable for the release of cholesterol. The liver cell contains more receptors in the membrane for LDL on its outermost layer as there is a lower cholesterol level inside the cell. The blood's level of cholesterol is lowered when these receptors attach to and remove LDL from the circulation. In addition to lowering cholesterol, statins also improve endothelial function, reduce C-reactive protein, stop platelet aggregation, and inhibit the growth of smooth muscle cells (Sirtori, C.R., 2014).

B. Side effects: Statins can result in stomach pain, gas, and constipation, despite their generally good tolerance. The concentrations of the liver enzymes ALT and AST increase in 1–5% of persons taking statins. If the level of at least one of the aforementioned enzymes in two consecutive readings is over three times the upper limits of normal values, the usage of a statin should be stopped. Whenever the enzyme level increases more moderately, it is sufficient to limit the drug's dosage reduction. Usually, enzyme levels quickly return to normal, enabling treatment to continue with a distinct statin. Myopathy and myalgia, which induce muscle soreness and fatigue and are correlated with a more than five-fold rise in creatine phosphokinase levels, are unusual (0.1-0.5%) side effects of statin therapy that necessitate quitting the prescription. Rhabdomyolysis with probable renal tubule injury, is the most dangerous side effect of statin treatment. The complication is followed by a greater than ten-fold rise in the myoglobinuria, causing the urine to darken in colour. As soon as rhabdomyolysis (renal failure) begins, statins should be stopped (Sirtori, C.R., 2014).

7.2. FIBRATES

These lipid-lowering drugs lessen the chance of heart disease and early coronary artery disease in lipid disorders such as that brought on by type-2 diabetes and the metabolic disorder (Chapman, M.J., 2003). Fibrate therapy is believed to be beneficial for patients with mild to high heart risk, particularly individuals with elevated levels of lipids and low good cholesterol levels (Kim, N.H. and Kim, S.G., 2020).

A. Mechanism of Action: Agonists of Peroxisome proliferator-activated receptors are intracellular elements that contain a group of enzymes and are classified as fibrates, a class of nuclear receptors. These enzymes' activation enhances cellular nucleus functions, including regulating fatty acid oxidation, apoprotein production, and lipoprotein metabolism. Utilizing these procedures reduces the plasma levels of VLDL by

activating plasma lipoprotein lipases, which are enzymes that regulate the breakdown of VLDL (Sahebkar, A., *et al*., 2017).

B. Side effects: Even while fibrates are usually tolerated well, 5–10% of people may have negative side effects include headaches, sleeplessness, rashes, itching, abdominal pain, constipation, diarrhoea, and flatulence. Therapy does not need to be discontinued because these side effects are not severe. Long-term fibrates are not recommended for people with gallstone disease because they may increase the mitogenicity of bile. AST and ALT alkaline phosphatase levels are often decreased, while liver enzyme levels may increase. Combining fibrates and statins increases the risk of myopathy, myalgia, and elevated liver enzymes (Akob, T., *et al*., 2016).

7.3. BILE ACID SEQUESTRANTS

Bile acid sequestrants, sometimes referred to as ion exchange resins, have been extensively used as lipid-lowering drugs for about 30 years. Clinical trials have shown their effectiveness in reducing myocardial infarction deaths and cardiovascular complications. Research on these drugs' ability to cure atherosclerosis is currently underway, despite the fact that they are no longer utilized in clinical settings (Miller, M.L., Wright, C.C. and Browne, B., 2015).

A. Mechanism of action: Ion-exchange resins bind cholesterol, which metabolizes bile acids within the lumen of small intestine and facilitates their evacuation with faeces. Two examples of representative resins are colestipol and cholesterol (Meissner, M., *et al*., 2013)

B. Side effects: Ion exchange resins frequently cause constipation, gas, and dyspepsia as side effects, and many individuals hesitate to consume them because of their flavour. To avoid a decrease in their absorption, ion exchange resins are given either 1-2 hours before or 4 hours after the administration of digoxin, warfarin, thiazide diuretics, and β-adrenergic blockers (Yu, B., *et al*., 2014).

7.4. CHOLESTEROL ABSORPTION INHIBITORS

The most widely used medication of this kind is ezetimibe. It stops cholesterol from passing through the intestinal wall by blocking the absorption of dietary and biliary cholesterol as well as associated phytosterols in the intestine (Catapano, A.L., 2001). Its combination with simvastatin intensifies ezetimibe's lipid-lowering action.

A. Mechanism of action: By specifically preventing the ingestion of bile lipids and lipids in the villi, ezetimibe lowers the amount of cholesterol that travels from the intestinal tract to the liver, the quantity of lipids in the cells of the liver, and the quantity of lipids that is removed from blood plasma (Howles, P.N., 2016).

B. Side effects: There is good tolerance to ezetimibe. The drug may cause an increase in serum transaminases, especially if statins are taken concurrently. Ezetimibe and statins should not be used together in people with acute liver sickness or liver enzyme levels that are three times higher than usual. Concurrent administration of cyclosporine can significantly increase the plasma levels of ezetimibe (Tonstad, S., 2017).

7.5. NICOTINIC ACID

Nicotinic acid has several beneficial effects on lipid metabolism. The Coronary Drug Project long-term trial found that the only patients who took niacin over the long term had an 11% lower overall mortality rate than the placebo group (Meyer-Ficca, M. and Kirkland, J.B., 2016).

A. Mechanism of action: By decreasing the production of VLDL in liver and partially blocking expulsion of fatty acids from adipose tissue, nicotinic acid results in a plasma deficit.

B. Side effects: Adverse effects, including hot flushes and a noticeable swelling of the face and upper torso, are often seen with nicotinic acid acceptance. The reaction is brought on by active prostaglandin release that is triggered by nicotine. Side effects may be significantly reduced by administering 0.5 g of aspirin 30 minutes before taking nicotinic acid and gradually increasing its dosage. When endurance is prescribed, side effects are less frequent. Up to 5% of individuals may experience abdominal pain as one of the side effects, which

may be connected to an exacerbation of their gastritis. However, the most serious and uncommon outcome is the onset of liver failure. Hepatic insufficiency manifests as a hepatic coma clinic, a rapid drop in lipids, and a dramatic increase in liver enzyme levels. Caution should be used when consuming nicotinic acid with fibrates or statins. Since nicotinic acid may worsen the condition that is underlying in 5–10% of gout patients, they should avoid giving any sort of it (Blond, E., Goudable, J. and Laville, M., 2015).

VIII. EMERGENT REMEDIES

8.1. Therapy Targeting Cytokines:

Since, the role of swelling in the progression of the disease has been established, strategies that target pathways of inflammation have become promising new therapeutic alternatives (Poznyak, A.V., *et al*., 2021).

A. Anti-IL-1 Agents

The cytokine IL-1 is implicated in all phases of hyperlipidemia and is a harmful agent in instability of plaque. It increases vascular smooth muscle cell growth and development, enhance adhesion molecule expression, and stimulates macrophages, which release Matrix Metalloproteases and interleukins (IL-6), two proinflammatory mediators (Mai, W. and Liao, Y., 2020). Cryopyrin-related periodic syndrome, adult-onset Still's disease, systemic juvenile idiopathic arthritis, and familial Mediterranean fever can all be treated with canakinumab. By attaching itself to IL-1 and blocking its interaction with the IL-1 receptor, it neutralizes IL-1 signalling (Gram, H., 2020). Canakinumab may increase the chance of infections and encourage plaque instability, despite its outstanding safety record (Mai, W., and Liao, Y., 2020, Soehnlein, O., and Libby, P., 2021). Another well-known IL-1 blocker is Anakinra, a recombinant IL-1 receptor antagonist which is utilised for the treatment of arthritis (Gram, H., 2020). During clinical trials, anakinra decrease the acute inflammatory response. Although, because of adverse consequences of frequent use, the drug is not suitable for treating chronic illnesses (Mai, W. and Liao, Y., 2020).

B. Anti-IL-6 Agents

IL-6 is a potent, cytokine that indicates inflammation and is related to a high risk of heart disorders. High IL-6 levels are related with amplified heart events. Additionally, coronary artery disease is accelerated by IL-6 (Lindmark, E., *et al*., 2001, Reiss, A. B., *et al*., 2017). Tocilizumab is a monoclonal antibody that stops IL-6 from binding to its own receptors on different kinds of cells. It is recommended for people with mild to chronic arthritis as it decreases inflammatory responses (Broch, K., Anstensrud, A. K., Woxholt, S., *et al*., 2021). Unfortunately, by lowering the amounts of low-density lipoprotein receptors, tocilizumab negatively changes the lipid profile by increasing TG and low-density lipoproteins. Ziltivekimab, an antibody which targets the IL-6 ligand, is now studied as a treatment for atherosclerosis. Ziltivekimab administered subcutaneously dramatically reduced systemic thrombosis and inflammatory biomarkers that are known to encourage the atherothrombotic process in individuals with high risk factors for cardiovascular disease (Ridker, P.M., *et al*., 2021).

C. Anti-TNF-Agents

Tumor necrosis factor (TNF) is a regulator of immunological responses and a significant contributor to hyperlipidemia. Dysfunction of endothelial barrier is caused by a number of factors, including increased vascular permeability, decreased bioavailability of nitric oxide, high release of reactive oxygen species, and movement in the vascular wall. Additionally, it alters the function of smooth muscle cells by increasing its growth (Urschel, K. and Cicha, I., 2015). TNF-inhibitors, however, did not offer any clinically meaningful benefits to patients suffering from severe cardiovascular disease. There are currently no clinical trials investigating the usage of anti-TNF medications in people who are at high risk for cardiovascular disease (Ji, E. and Lee, S., 2021, Tousoulis, D., *et al*., 2016).

8.2. Anti-P-Selectin Therapy:

Over the surface of active platelets and endothelial cells, this molecule is strongly expressed. P-selectin encourages production of proinflammatory cytokines, the development of thrombus, and the involvement and adherence of leukocytes to the walls of arteries (Woollard, K.J. and Chin-Dusting, J., 2007). Inclacumab is a highly promising completely human IgG4 monoclonal antibody that inhibits P-selectin. In patients with cardiovascular disorders, it has anti-cell adhesion, anti-inflammatory, and anti-thrombotic properties along with inhibiting P-selectin activity (Gluba-Brzozka, A., *et al*., 2021). New clinical trials are planned, and the medication seems to be well tolerated (Geng, X., *et al*., 2020).

8.3. Angiopoietin Like Targeting Agents (ANGPTL3):

Angiopoietin Like Targeting Agents is a protein that belongs to the angiopoietin-like protein family. Because of its part in metabolism of human lipoprotein through the blocking of lipoprotein and endothelium lipases, ANGPTL3 has become desirable target in cardiac therapy (Ruhanen, H., *et al*., 2020). Inhibiting Angiopoietin Like Targeting Agents activity results in a considerable decrease in all types of lipoproteins, and Angiopoietin Like Targeting Agents loss-of-function variants have been related with a protective effect in contradiction of cardiac illnesses, lowering chance of heart attack or stroke by 34% (Stitziel, N.O., *et al*., 2017). Evinacumab inactivates circulating Angiopoietin Like Targeting Agents by interacting with the protein. It decreases cholesterol levels and boosts the removal of triglycerides-rich lipoproteins. The combination of atorvastatin, alirocumab, and evinacumab reduced the formation of plaques by decreasing size, number, and development of macrophages in plaque (Pouwer, M.G., *et al*., 2020).

8.4. Photodynamic Therapy (PDT):

PDT is a recent method used to cure a variety of malignant, non-cancerous, and infectious ailments. In recent years, it has drawn consideration as a possible treatment for atherosclerosis. It induces atherosclerotic plaques to settle and retreat while also promoting vascular healing. Depletion of macrophages, a decrease in composition of foam cells, and the regrowth of plaques are some of the impacts of PDT on plaque stability. It can also prevent restenosis during the coronary angioplasty. The method involves the involvement of three parts: photosensitizer, molecular oxygen, and light with a certain wavelength. The photosensitizer preferentially aggregates in atherosclerotic lesions following light activation, where it aggravates a photochemical reaction that disrupts cell survival and remodelling processes and generates reactive oxygen species (ROS) (Jain, M., *et al*., 2017, Benov, L., 2015, Correaia, J. H., *et al*., 2021). Polymer nanoparticles, liposome-based formulations, and self-assembled protein nanostructures were suggested as possible delivery vehicles. Furthermore, coupling with other ligands for receptors of macrophage surface dextran or class A scavenger receptors may improve photosensitizer targeting. Significant developments in laser technology may potentially help optimize PDT and its use in clinical settings (Jain, M., *et al*., 2017, Benov, L., 2015, Houthoofd, S., *et al*., 2020).

8.5. Theranostics:

A new method called "theranostics" integrates diagnosis and treatment into a single delivery mechanism. Even though theranostics' use in cardiovascular diseases remains in its infancy, research on the manufacture of these compounds is growing and the area has received more attention. Theranostics medicine enables targeted treatment, improved drug effectiveness, and effective, image-guided, and customized illness therapy (Geetha Bai, R., *et al*., 2015). This therapy of atherosclerosis and vascular diseases has been studied using a variety of nanocarriers (Bejarano, J., *et al*., 2018, Agrawal, S., *et al*., 2021, Wu, Y., *et al*., 2021).

MRI contrast agents were the main reason for the development of solid lipid nanoparticles, nanoparticles of iron oxide, nanocomposites of cerium oxide and iron oxide, nanoparticles of paramagnetic perfluorocarbon combined with fumagillin (Oumzil, K., *et al*., 2016). They conjugated to antibodies which target macrophages to show that they could see atherosclerotic plaques (Chen, J., *et al*., 2020, Nandwana, V., *et al*., 2017). Macrophages are naturally drawn to atherosclerotic plaque, and HDL-like nanoparticles did not trigger any immunological responses. They promoted atherosclerotic plaque regression and cholesterol efflux. Iron nanocomposites quenched ROS in inflammatory macrophages, while theranostics systems that included MRI, solid fatty acid nanoparticles, and ultrasmall superparamagnetic iron oxide particles encapsulated with prostacyclin prevented platelet deposition (Oumzil, K., *et al*., 2016). In order to develop clinically acceptable theranostics, more research is required to address certain issues associated to layout, systemic poisoning and strength of nanomaterials, the utilization of experiments that are nearer to human coronary artery disease and industrial production, even though theranostics offers quick and simple evaluation of cardiovascular disease in animal models (Wu, Y., *et al*., 2021).

CONCLUSION

A major concern for global wellness, hyperlipidemia is a complicated, multifaceted disease. The necessity for a thorough grasp of hyperlipidemia's epidemiology, pathology, etiology, comorbidities, evaluation methods, and treatments is highlighted by the disease's rising prevalence worldwide. The worrying increase in hyperlipidemic rates, which are more common in industrialized nations, is highlighted by epidemiological data. Developing countries are not exempt, though, as a result of changing lifestyles. Atherosclerosis has a complicated etiology and pathophysiology that involves the interaction of behavioural, environmental, and genetic factors. It emphasizes that being hyperlipidemic is not just a result of eating too much or not exercising enough. Hyperlipidemia has several side effects that impact practically every organ system in the body. A multifaceted strategy is required for the treatment of hyperlipidemia, including medication, lifestyle changes, physical exercise etc. There is now hope for improved management of hyperlipidemia which have completely changed the therapy landscape. It necessitates further research to unravel the complex pathophysiology of atherosclerosis and develop more effective therapeutic strategies. The fight against hyperlipidemia is a long one, but with concerted efforts from researchers, clinicians, policymakers, and individuals, it is a battle that can be won.

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