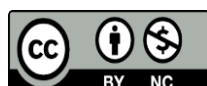


Apolipoproteins and cardiovascular disease: Risk factors, biomarkers, and potential treatments

Ramanpreet Kaur¹, and Priya Chaudhary^{ID}¹ ✉

¹Department of Biotechnology, School of Applied and Life Sciences, Uttarakhand University, Dehradun (248007), Uttarakhand, India.

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Abstract: Reducing cardiovascular risk requires effective and economical medicines, as cardiovascular disease is the primary reason of fatality and morbidity globally. While low density lipoprotein (LDL) is linked to higher chances of coronary heart ailments, atherosclerosis may also be influenced by other lipoproteins and the apolipoproteins that make them up. Higher heart attacks are linked to higher amounts of apolipoprotein (apo) B, an element of atherogenic lipoproteins, and a decreased amount of apo A-I, a constituent of anti-atherogenic high density lipoprotein (HDL). It has been shown that apo A-I, apo B, and the apo A-I/apo B ratio are more accurate indicators of coronary artery disease, and they even continue to be so in individuals undergoing lipid-modifying treatment. The assessment of these apolipoproteins may enhance the forecasting of cardiovascular risk. The first-line treatment for high cholesterol is the use of statins to inhibit the manufacture of cholesterol. However, in certain cases, other lipid-lowering drugs are needed to achieve desired concentration of LDL cholesterol. In the context of heart disease, this review provides a thorough discussion of different risk factors of cardiovascular disease, low- and high-density lipoprotein cholesterol and their involvement in pathological action that impact cardiovascular system along with clinical implications of apolipoproteins. Additionally, a summary of potential mechanisms of the cardioprotective effects of HDL and apo A-I with current and novel therapeutic processes to lessen the impact of lipid-induced cardiovascular disease is also given.

Keywords: Cardiovascular ailment; Apolipoproteins; Atherosclerosis; High density lipoprotein (HDL); Low density lipoprotein (LDL); Statin

1. Introduction

Extensive cardiovascular investigation studies and the genetics of human research disagree with the idea that high-density lipoprotein (HDL) cholesterol causes the development of coronary artery disease (CAD). Low-density lipoproteins (LDL) are among the main lipids in atherogenesis, vital in cholesterol transportation. Modifying the level of lipids has grown into one of the important targets for cardiovascular prophylaxis, specifically decreasing the likelihood of cardiovascular disease (CVD) by attacking LDL-cholesterol with various reducing agents [1].

Nutrition, vigorous activity, and smoking are all basic indicators of risk for coronary artery disease that can be tackled with therapies. Beginning and staying with these lifestyle modifications are difficult challenges. Luckily, the

statin group of medicines is especially successful at lowering heart attacks, even in people with ordinary LDL levels. Numerous research investigations on a broad spectrum of people have found that lipid-lowering medications decrease heart attacks by 25% to 38%. Interestingly, statins and additional lipid-lowering medications had a far smaller influence on the amount of stenosis induced by a plaque, on the scale of just a few percentage points [2].

However, individuals with inadequate LDL lowering from statin medication or statin resistance need supplementary or other therapeutic alternatives. In addition, recent results advised expanding the scope outside HDL and LDL to lipoproteins A and B [3]. In this article, we will look over CVD, risk factors for CVD, the mechanisms of LDL and HDL, and apolipoproteins with CVD, offering mechanical explanations for their function in CVD and discussing ways to treat CVD to lower the lipid-induced heart disease burden.

2. CVD and its risk factors

Worldwide, CVD is the primary cause of ailments and death. After extensive treatment, this pattern is predicted to persist, and yearly deaths will increase to about twenty-four



Dr. Priya Chaudhary
Department of Biotechnology,
School of Applied and Life Sciences, Uttarakhand University,
Dehradun, Uttarakhand – 248007, India
E-mail: priyachaudhary@uumail.in

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million by 2030 [4]. Lipids build up in the walls of arteries, causing inflammatory reactions that are responsible for the onset of atherosclerosis. Disorders in the circulatory system can lead to a variety of issues, including heart failure, often known as cardiovascular disease (CVD), which is comprised of four different entities [5] as discussed in Table 1.

Table 1. Different types of cardiovascular diseases.

Types	Characteristics
Coronary artery disease (CAD)	This condition is brought on by a reduction in myocardial perfusion that can lead to cardiac failure, myocardial infarction (MI), and/or angina. It is responsible for between one-third and half of CVD events.
Cerebrovascular disease	Comprising transient ischemic attacks (TIAs) and stroke
Peripheral artery disease (PAD)	Especially limb-related vascular disorders that might cause cramping.
Aortic atherosclerosis	Include aneurysms in the abdomen and thorax.

Cigarette use, high blood pressure, diabetes, aberrant lipid profiles, being overweight, and lack of exercise are the primary risk variables of CVD. Seasonal and geographic shifts in these established risk variables are linked to deviations in CVD rates worldwide [6].

2.1 Smoking and alcohol consumption

Additionally, there is increasing proof that e-cigarettes, which the tobacco sector is currently actively pushing, hurt the cardiovascular system. Therefore, the ultimate objective of medical policy should be to entirely eradicate the consumption of tobacco goods in any form. Most nations have seen a consistent decrease in the number of people who consume tobacco products. According to present research, 31% of mature males and 6% of mature females worldwide consume tobacco-related goods regularly [7]. However, there are significant regional and, particularly, sex and socioeconomic class-based variations in smoking trends. While tobacco has decreased in many high-income countries (HIC), it is still highly prevalent among males in China, Europe, Russia, and some regions of South America. In HIC, tobacco is more prevalent among men in the lowest economic categories. Women have not, however, repeatedly shown this tendency [8]. Additionally, many nations in South America, Europe, East Asia, the Middle East, and the East report high rates of tobacco use as well as a substantial mean use of cigarettes (>20/d) among those who smoke [9]. Matsuo et al. (2020) reported that those who stopped smoking within the first two years of a stroke had a higher risk of poor functional results compared to nonsmokers [10]. For current smokers, the risk of having a

negative functional result tended to increase with regular cigarette usage in the Western Pacific region of Japan. Alotaibi et al. (2021) reported that smoking reduces postprandial metabolism and is a recognized significant cause for coronary heart disease in the European region of the United Kingdom [11]. Consuming too much alcohol is not only an economic problem, but it also considerably raises disease and death rates in numerous neighborhoods. The findings of predictive investigations have substantially confirmed those of clinical trials. Alcohol addicts have a higher probability of dying from any reason. It was noticed that those who experienced cardiac arrest more commonly drank alcohol in the final moments of their lives than those who perished from other types of CVD [12]. The findings of the British Regional Heart Study corroborated this consistency, revealing that the rate of cardiac arrest amongst those who drank alcohol was around twice as high as among non-alcoholics. Even if heart disease was not identified, older men had the highest rate of unexpected deaths [13]. Drinking too much alcohol has been linked to an elevated likelihood of atrial fibrillation, but its root causes are unknown. An expanded left atrium and decreased left atrial activity might result in atrial fibrillation [14]. In a separate analysis of this information, Zhang and colleagues discovered a J-shaped connection between alcohol consumption and stroke [15]. Consuming 0 to 20 g/day (or <2 drinks) was linked to a reduced likelihood of stroke, including total, ischemic, and hemorrhagic strokes, as well as stroke death. However, alcohol use of more than 30 g per day (more than two drinks), and especially more than 45 g per day (more than three drinks), was linked to a higher likelihood of all stroke results.

2.2 Blood pressure

Even slight rises in blood pressure (BP) within normal limits are associated with a stepwise rise in the likelihood of CVD. But in initial prevention, BP decrease has only been demonstrated to accurately reduce the likelihood of CVD in individuals with developed high BP; aiming for a reduced systolic blood pressure of 120 mm Hg has been proven to be beneficial in individuals at elevated cardiovascular risk, which includes those with developed vascular illness [16]. Moreover, several blood pressure-lowering medications, including blockers and angiotensin-converting enzyme (ACE) inhibitors, reduced CVD in those at increased risk regardless of whether their blood pressure is not within the range of hypertension; this has not been seen in people without CVD [17]. According to the results of a meta-analysis, for each person, participant-level information collected from 48 randomized clinical trials, including 344,716 subjects with an average age of 65 years, the corresponding decrease in the likelihood of developing serious heart attacks was equivalent to the level of blood pressure decrease. Each 5-mmHg drop in systolic blood pressure reduced the likelihood of heart attacks by 10% [18].

2.3 Cholesterol

A stepwise rise in events related to CVD is linked to a greater atherogenic lipid load, which is determined by measuring the amount of LDL, total cholesterol, or apo B; or the proportion of total cholesterol/HDL, or apo B/apo A-I. Additionally, a lower level of LDL decreases the likelihood of CVD, and this impact is constant throughout the previous LDL threshold region [1]. It is anticipated that a 1 mmol decrease in LDL cholesterol levels over five years in persons can lead to a twenty percent decrease in CVD risk. The amount of decrease in CVD is proportional to the level of decrease in LDL cholesterol. Globally, men and women were predicted to have median total cholesterol values of 4.64 and 4.76 mmol/L, age-standardized [19]. Serum amounts of cholesterol have slightly decreased (by $\approx 4\%$) in most of Europe, Australia, and North America over the last forty years, although these parts of the world still have the greatest average levels of total cholesterol globally. Average levels of cholesterol in individuals have been rising significantly in South Asia, South East Asia, and East Asia during the same period [20].

2.4 Diet

Cardiac disease nutritional variables are typically divided into three categories: eating habits, food categories (such as vegetables, fruits, nuts, whole grain foods, and lentils), and nutrient content of food (such as monounsaturated and

sugars, added sodium chloride, harmful fats, and animal-derived foods, while poor in nutritious vegetables, fruits, lentils, seafood, and nuts. They are frequently loaded with manufactured food products, typically packed and frequently readily available to consume, but low in nutrition [22]. Up to 50% of the sugar that is added to the diet of Americans is linked to their consumption of drinks with sugar. There is a substantial epidemiologic correlation between sugar use, being overweight, high BP, and diabetes. The risk ratio (RR) for a 1-helping rise in sugar per day was found to be 1.17 for CVD and 1.08 for hypertension at the time of prospective investigations of sugar and high blood pressure, CVD, and stroke [23].

2.5 Physical inactivity

Through the World Health Assembly's Global Health Observatory, uniform measurements of total aerobic activity (taken from the worldwide or universal physical movement survey) were gathered in 122 different nations. These statistics are used to figure out the percentage of grownups (over the age of 18) who are not physically active, which is characterized as engaging at least five days a week in moderately strenuous activity for a minimum of thirty minutes, three days a week in high-intensity exercise for at least twenty minutes, and accumulating a total of less than 600 metabolic processes comparable minutes per week from all kinds of exercise [24]. Generally speaking, women are less physically active than men. The eastern

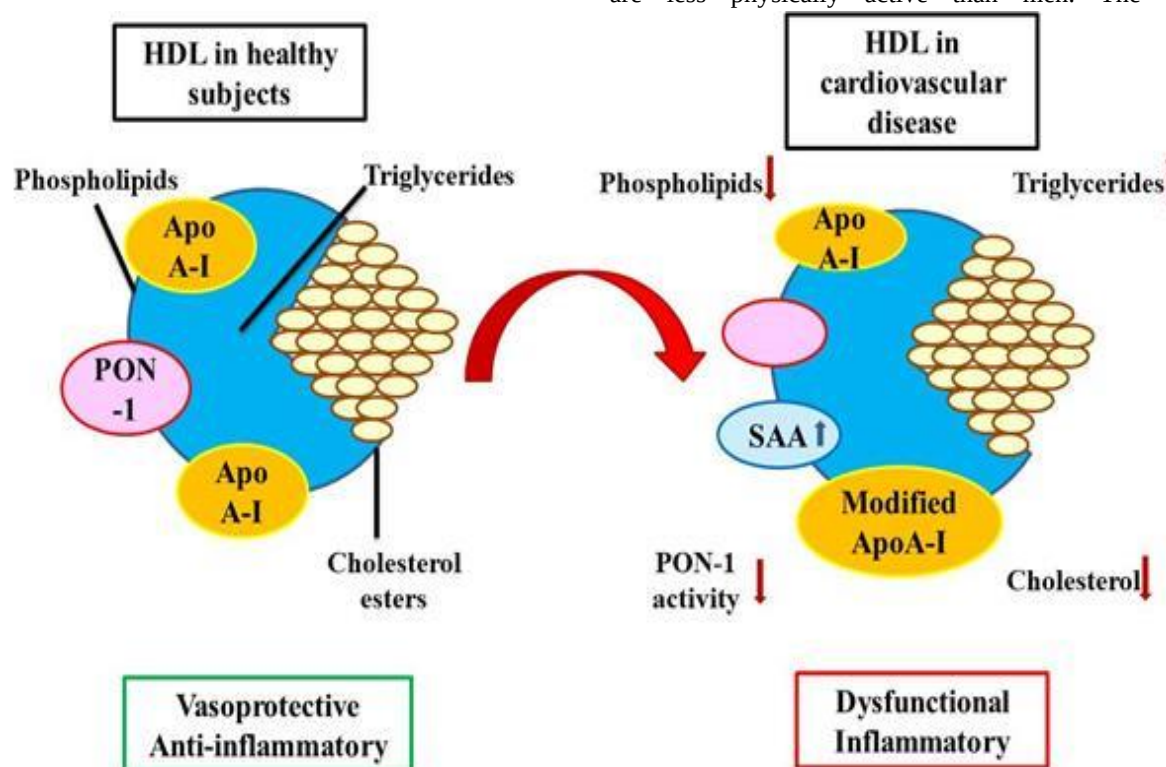


Figure 1. Scheme representing the relation of HDL, apolipoprotein A-I and cardiovascular risk.

saturated fat). Moreover, many studies have concentrated on fats in the diet, given the scientifically proven connection between serum levels of cholesterol and CVD risk [21]. Poor-quality foods are filled with processed grains, refined

Mediterranean and the Americas have the greatest rates of inactivity among adults. Furthermore, compared to men, women in many African nations have abnormally substantial levels of physical inactivity. The Americas and

Europe have also been found to have the greatest rates of sedentary lifestyles, which are characterized by spending more than four hours a day in chairs [25].

3. Factors responsible for the onset of CVD

3.1 HDL, apolipoprotein A-I, and cardiovascular risk

Apolipoproteins are proteins found in lipoprotein particles that have been linked to lipids. Apolipoproteins play important roles in the breakdown of lipoproteins, including transporting these substances into the plasma, attaching to specific surface receptors on cells to accurately govern lipids toward targeted organs and tissues in the body, and activating or inhibiting lipid metabolism-related enzymes [26].

Apolipoproteins A-I and A-II are the main lipoprotein components of HDL. While apo A-II has been associated with an increased risk of atherosclerosis in studies on animals, apo A-I is the primary apo in HDL, making up 70% of all HDL-related proteins and mediating several of the anti-atherogenic activities of HDL (Figure 1). Generated in the intestines along with the liver, apo A-I is in charge of starting the process known as reversing the transport of cholesterol for removal [27]. Individuals with apo A-I values less than 1.2 g/L have a greater likelihood of developing CVD in comparison to those with levels greater than 1.6 g/L. Similar to LDL, various patient types have different levels of cholesterol in HDL particles, which is regulated by plasma TG levels; individuals who have elevated TG typically have lower apo A-I concentrations. However, it is uncertain if apo A-I by itself, apart from its relationship with HDL, is an indicator of CVD risk, as shown in Figure 1 [28]. Circulating apo A-I concentrations have been employed as a biomarker for HDL cholesterol levels, even though each HDL component includes five apo A-I types [29]. There is an ongoing debate over the connection between apo A-I and coronary heart disease. Apo A1 and the occurrence of coronary ailment are inversely correlated, according to a sizable meta-analysis in the population as a whole [30].

3.2 HDL heterogeneity and post-translational modifications

Human HDL is now known to consist of a highly diverse lipoprotein family with variations in weight, shape, size, and protein and lipid composition. In contrast to other lipoprotein groups, HDL is composed of an array of proteins that serve as its functional and structural foundation. Proteinase inhibitors, complement components, acute-phase response proteins, lipid transfer proteins, enzymes, and apolipoproteins are among the nearly one hundred proteins that have been found to interact with HDL to the present. These proteins distribute differently among HDL subpopulations [31]. In addition, modifications after translation, such as glycosylation, truncations, phosphorylation, and oxidations, frequently occur in the

majority of proteins. Several proteins that are altered or undergo post-translational modifications during an acute phase, including inflammatory response and damage to tissues, underlie the protective properties of typical, functional HDL. The HDL becomes a faulty HDL component with a decrease in its reverse transportation of cholesterol due to the decreased existence and activity of safeguarding, anti-inflammatory agents, as well as a rise in pro-apoptotic and pro-inflammatory molecules on the surface of HDL [32].

3.3 Apolipoprotein A-II, lipid metabolism, and cardiovascular risk

Autophagy is regulated by mechanisms such as the ApoA-II combines following lipid transferring and circulates as LpA-II. LCAT then mixes LpA-II with running LpA-I particles to produce LpA-I/A-II particles. In comparison to ApoA-I, ApoA-II does not trigger LCAT [33]. ApoA-II promotes HDL maturation, reverses cholesterol flow, and has antioxidant effects. The bulk of ApoA-II particles in HDL exist in combination with ApoA-I, with just a small percentage of HDL containing ApoA-II alone (LpA-II). The amount of LpA-I/A-II is constant independent of HDL quantity, showing that rises in HDL levels are ascribed to a rise in LpA-I, not LpA-I/A-II. Conflicting findings have been published regarding ApoA-II and the possibility of ASCVD. People bearing the APOA2 variation rs5082 (265T/C), which leads to reduced ApoA-II levels, have demonstrated a reduced likelihood of CAD [34].

3.4 LDL, apolipoprotein B and cardiovascular risk

As the main atherogenic lipoprotein, LDL is regarded as the main target for the treatment of coronary heart disease. Moreover, several lines of research suggest that additional TG-rich lipoproteins may also be atherogenic, for instance, very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). According to reports, almost 50% of individuals with atherogenic lipoprotein aberrations had a higher chance of developing CVD [35]. Apo B is a crucial constituent of various atherogenic lipoproteins, which include LDL, IDL, and VLDL (Figure 2). The testing of apo B was used to determine the concentration of this lipoprotein in an individual because each of the atherogenic lipoproteins contains at least one particle of apo B in its structure [36]. This resulted in apo B as a probable indicator of cardiac risk and fatality [37].

There are two different types of apolipoprotein B: apo B-100 and apo B-48. In the intestinal tract, apo B-48 is

generated. Apo B-100 and -48 are the two subtypes of apo B. The apo B-48 is synthesized in the intestinal tract and further combines with free cholesterol and TG, which further goes down to the lumen of the gut for the creation of chylomicrons. These chylomicrons are processed in both the liver and the bloodstream. Then, the liver results in the production of apo B-100, which is an important constituent

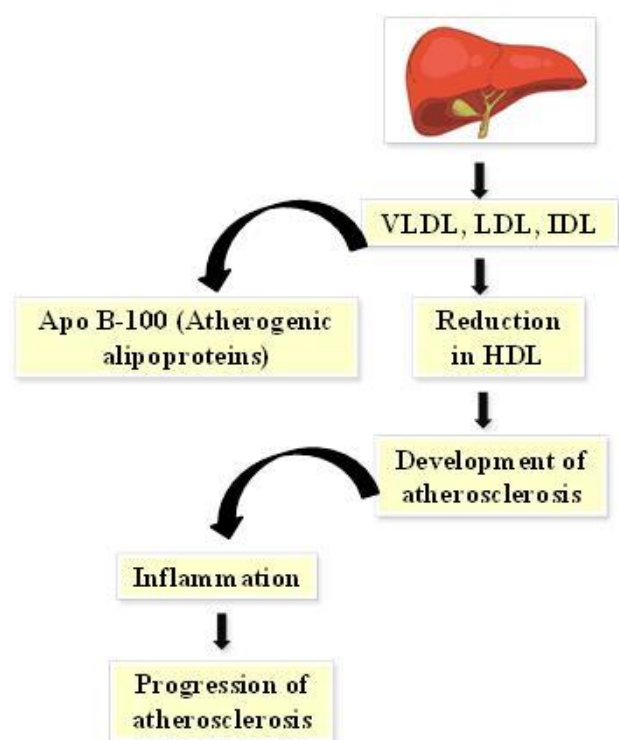


Figure 2. Role of apolipoprotein B-100 in the initiation and progression of atherosclerosis. VLDL: very low-density lipoprotein; LDL: low density lipoprotein; and IDL: intermediate density lipoprotein.

in LDL, IDL, and VLDL particles [38]. The liver is the site where VLDL is produced and released to create two further subtypes of VLDL that are VLDL1 (huge and triglyceride-rich) and VLDL2 (small and lower in triglyceride). When it comes to the atherogenicity of plasma lipoproteins, the kind of particle released is crucial. It has been demonstrated that the production of VLDL1 causes a reduction in HDL and a rise in so-called small, denser LDL; both of them are known to accelerate the development of atherosclerosis (Figure 2). Individuals diagnosed with diabetes and resistant to insulin exhibit elevated levels of VLDL1 [39]. VLDL is made up of a layer of amphipathic molecules like proteins, phospholipids, and free cholesterol that encircles an inner core of neutral lipids (triglycerides and cholesterol esters) [40].

Secretory peptide apo B-100 is produced on ribosomes that are affixed to the endoplasmic reticulum's interface. The "nascent" polypeptide is carried by a pathway from the ribosome's place of production across the cell membrane to the endoplasmic reticulum lumen (ER) during its development. In the ER, secretory proteins must fold to get their tertiary structure through a procedure known as chaperone folding of proteins [41, 42]. Vesicles that transport nutrients arrange properly with proteins folded into exit locations so they can leave the ER. The resulting protein is pulled back via the membrane channel, kept in the ER, and sorted for proteasomal destruction if the proper tertiary structure is not reached. Ionic interactions among the clustered basic amino acids in the apo B-100 that attach to the negatively charged glycosaminoglycans (GAGs) of

the protein peptides in the walls of arteries regulate the attachment of atherogenic lipoproteins to the latter [43].

Retention of LDL seems to entail an indirect connection between LDL and artery wall proteoglycans, aided by "bridging molecules," as well as the direct relationship between apo B-100 and these proteoglycans. With an apo E concentration of proteoglycan-binding faulty LDL, the defective direct connection between RK3359–3369SA LDL and arterial wall proteoglycans is replaced. Apo E is a powerful bridge factor connecting mutant LDL and arterial wall protein peptides [44].

4. Apo B to Apo A-I ratio as a biomarker

Lecithin-cholesterol acyltransferase (LCAT) is an enzyme that carries out the esterification of cholesterol present in the plasma and raises HDL's ability to transport cholesterol, which is activated by Apo A-I. The equilibrium between the two opposing forces is reflected in the apo A-I/apo B ratio, which is a reliable indication of CVD risk. More cholesterol circulates in the plasma and deposits itself into the artery wall when the ratio increases [45]. Apolipoprotein-related Mortality RISK (AMORIS) trial and INTERHEART research are two examples of future research that have demonstrated a beneficial linear connection between rising apo A-I/apo B ratio and the likelihood of a cardiovascular event. Individuals in the AMORIS trial who had experienced their first cardiovascular event before turning 50 years old showed higher levels of total cholesterol, LDL, hyperglycemia, apoB, triglycerides, and the apo A-I/apo B ratio in comparison to controls. This suggests the difference in levels of lipoprotein between those who are at an elevated likelihood of a cardiovascular incident at an early age and those who do not support treating and correcting this gap [1].

Sierra-Johnson et al. (2007) conducted a prospective investigation of appropriate multi-ethnic samples to assess CVD predictors [46]. Both apo B and the apo A-I/apo B ratio outperformed conventional cholesterol indicators in terms of accuracy when it came to predicting death from coronary artery disease according to apolipoprotein concentrations. They tested whether apo B/apo A-I was better than apo B by itself, and after controlling for risk variables, for instance, obesity, hypertension, diabetes, cigarette smoking, high C-reactive protein (CRP), and dyslipidemia, they discovered that the variance was not statistically noteworthy. Therefore, utilizing apo B/apo A-I over apo B alone did not appear to be beneficial. Researchers consequently concluded that apo B is the main cause of the strong predictive capacity of the apo A-I/apo B ratio and the lower significance of apoA1 in the risk evaluation. However, using apo B/apo A-I provides additional advantages. The apolipoprotein ratio may be beneficial for individuals whose phenotypes do not depend on apo B because it is linked to resistance to insulin in non-diabetic participants [47].

5. Potential mechanisms of the cardioprotective effects of HDL and apo A-I

The cardioprotective properties of apo A-I may be attributed to many processes, such as improved reverse cholesterol transfer, reduced oxidative stress, elevated peroxonase activity, and heightened anticoagulant activity.

5.1 Reverse cholesterol transport

Through a process referred to as "reverse cholesterol transport," the human body eliminates additional cholesterol from tissues and sends it to the liver, where the gallbladder either excretes the cholesterol or redistributes it to other organs. HDL is the primary lipoprotein engaged in this mechanism. The protein apo A-1 is first produced in the liver and intestines. Once in the circulatory system, it travels to peripheral organs like the heart. Apo A-1 binds with receptors such as ATP-Binding Cassette, Sub-Family A (ABC1), Member 1 (ABCA1) in hepatocytes, enterocytes, and macrophages that inhabit veins and arteries [48].

When this protein interacts with macrophages, the body's immune phagocytes, which specialize in breaking down particles, cholesterol, and certain other lipids (phospholipids), are drawn to the apo A-I molecule. This mechanism results in the production of pre- β HDL, or nascent HDL molecules that are capable in interacting with Scavenger receptor class B member 1 (SR-B1) and ATP-binding cassette, sub-family G, member 1 (ABCG1) for the incorporation of more amount of cholesterol and results in the formation of the fully mature HDL molecule (α -HDL) by the help of LCAT enzyme [49]. Meanwhile, the transportation of cholesterol in hepatic cells was carried out in two different ways: indirectly and directly. In the primary process, the mature HDL and liver SR-B1 are involved in the transportation of a large amount of cholesterol. These mature HDL molecules exchange monomers of triacylglycerol for the cholesterol molecules of apo B-100, mainly LDL, with the help of cholesteryl ester transfer protein (CETP). Finally, these lipoproteins transport cholesterol to the hepatic region after binding with receptor of liver [50].

5.2 Vasodilatory and vaso-protective effects

High-density lipoproteins are capable of providing protection against the atherogenesis by stimulating the activation of endothelial nitric oxide synthase (eNOS). This activation is related to the activation of S1P and SR-B1. The binding of Src tyrosine kinase to the receptor of SR-B1 of endothelial HDL directs the activation of eNOS through MAPK and PI3K signaling. The activated S1P promotes PI3K/AKT/eNOS signaling pathway, whereas it restricts NF- κ B signaling and related expression of adherence protein [51]. The proliferation and movement of endothelial cells and the restriction of apoptosis and expression are all directed by the HDL-induced eNOS. Moreover, the

formation of endothelial progenitor cells, vasodilation, and raised integrity of endothelial barriers are some of the preventive ways to deal with CVD caused by HDL-directed nitric oxide [52].

5.3 Anti-thrombotic effects

In addition to reducing platelet susceptibility to stimulation, HDL also prevents stimulus-induced activation of platelets, which reduces the aggregation of platelets, and thrombus bulk, and delays the development of thrombus. By eliminating extra cholesterol from platelets' plasma membranes and limiting platelet cholesterol overload, HDL has been shown to reduce the activation of platelets. Additionally, endothelial cells' generation of nitric oxide is stimulated by HDL, which counteracts the activation of platelets [53]. Additionally, HDL modifies the process of coagulation by interfering at several points to regulate anti-thrombotic effects. The inhibitory effects of plasminogen activators (PAI-1) (which cleaves fibrin by plasminogen) and HDL have an inverse relationship with fibrin clot permeability, indicating that HDL prevents the development of thrombus by encouraging fibrinolysis [54].

Because Apo A-I shares structural similarity with the stabilizing factor prostacyclin (PGI₂), it may have anti-clotting properties. Its alpha-helix configuration allows it to attach to PGI₂, an initially unstable molecule, stabilizing it in the process and providing significant anti-aggregatory defence against the generation of platelet thrombin at areas of vascular injury. As thus, it advances its unique anti-atherogenic role in preventing coronary artery disease [55].

6. Clinical implications of apolipoproteins

A meta-analysis of 12 revealed epidemiological investigations that included predictions of the corresponding risks of apoB and non-HDL-C for CVD determined that within 10 years, a non-HDL-C method would avoid 300,000 events more than an LDL-C approach, while an apoB100 method would prevent 500,000 further occurrences than a non-HDL-C technique [56]. A meta-analysis of 12 revealed epidemiological investigations that included predictions of the corresponding risks of apoB and the latest Mendelian randomization experiments have shown that ApoB-100 is causally connected to an increased likelihood of heart failure, coronary artery disease (CAD), and coronary heart disease (CHD). ApoB genetic variations have also shed light on the protein's impact on cardiovascular risk. For instance, a faulty low-density lipoprotein receptor accounts for 90-95% of familial hypercholesterolemia (FH). However, in a small percentage of instances (5-10%), FH is caused by a faulty ApoB-100 variation, which has been linked to raised LDL-c levels and an increased risk of atherosclerotic CVD. This is produced by a decreased affinity for binding of mutant ApoB-100 to the LDLR, which hinders the elimination of LDL particles from the bloodstream [22]. Genetic investigations, including the Mendelian randomized model, provide proof

of causality between disease and elevated levels of lipoprotein(a). Mendelian randomization research depends on an arbitrary distribution of genetic variants at creation to make sure that both known and unidentified covariates are distributed evenly between genotype-defined comparison groups. Thus, research showing that lipoprotein genetic variations that are substantially linked to lipoprotein(a) levels are likewise related to CV risk gives proof of causation. The reported relationships are most likely without interference and cannot originate from causality that is reversed, as sickness cannot change inherited genotypes [57].

7. Treatment available for CVDs

Drugs for coronary artery disease (CAD) come in a variety of forms and combinations; some of these are covered below:

7.1 Anticoagulants

Blood thinners, or anticoagulants, are medications that aid in preventing blood clots. They are administered to patients who have a greater risk of blood clots to decrease their likelihood of experiencing life-threatening ailments like cardiac attacks and strokes. If a person has just had surgery, they could also be given an anticoagulant because the time of rest and immobility throughout the healing process might raise the possibility of blood clot formation [58]. Warfarin (Coumadin), heparin (various), rivaroxaban (Xarelto), edoxaban (Savaysa), dabigatran (Pradaxa), and apixaban (Eliquis) are a few that are frequently prescribed [59].

Because of their quick onset of antithrombotic activity, unfractionated heparin (UFH) and heparin of lower molecular weight are the preferred anticoagulants in acute cases of thrombosis [60, 61]. Three new oral anticoagulants, rivaroxaban, apixaban, and dabigatran, offer significant improvements over existing medications. Myocardial infarction, stroke, and ventilator-associated peripheral encephalopathy (VTE) are the three primary causes of cardiovascular mortality. Clinical trials including these medications have been successfully concluded. When compared to either LMWH or warfarin, novel medicines have demonstrated a decrease in thrombosis, severe bleeding, and side effects [62].

7.2 Antiplatelet agents and dual antiplatelet therapy

Blood clots are formed when platelets, which are tiny blood particles, group together. These thromboses have the potential to cause a heart attack and an abrupt clotting of a coronary stent. Two kinds of antiplatelet medications are utilized for treating a large number of stroke and heart attack victims, as well as those who want to prevent these events. This is known as dual antiplatelet treatment, or DAPT. If dual therapy is required, a mixture of aspirin and clopidogrel may be chosen [63]. There are two types of antiplatelet drugs: parenteral and oral. The mode of administration further subdivides oral medications. Aspirin

is an inhibitor of cyclooxygenase and the original antiplatelet agent. Dipyridamole, cilostazol, pentoxifylline, prasugrel, clopidogrel, and ticagrelor are further oral antiplatelet medications. Tirofiban and eptifibatide, two examples' inhibitors of glycoprotein IIb/IIIa that are only administered intravenously and are employed to treat acute coronary syndrome [64, 65].

7.3 Angiotensin-converting enzyme (ACE) inhibitors

When treating renal and CVDs, for instance, hypertension, diabetes, nephrotic syndrome, acute coronary syndrome, and heart failure, angiotensin-converting enzyme inhibitors are the most often prescribed drugs. An ACE inhibitor lowers the chance of experiencing a heart attack. They facilitate the heart's function by opening blood channels [66].

7.4 Different roles of ACE inhibitors

7.4.1 Hypertension

In individuals, angiotensin-converting enzyme inhibitors are capable of reducing the blood pressure of mean arterial pressure in addition to diastolic and systolic BP. In various randomized investigations, ACE inhibitors are successfully utilized as antihypertensive drugs [67]. ACE inhibitors are among the four types of medications that are advised for the initial treatment of people with increased blood pressure, according to scientific recommendations for managing high arterial pressure in men issued by the Eighth Joint National Commission (JNC8) in 2014. The other three pharmacological classes, including calcium channel blockers, thiazide diuretics, and angiotensin receptor blockers, are helpful as first treatments for the majority of non-Black people. For the majority of black individuals with increased BP, the sole suggested primary therapies are calcium channel blockers and thiazides [68].

7.4.2 Heart Failure

By raising renal circulation and decreasing the production of antidiuretic hormone and aldosterone, ACE inhibitors direct the increase of salt outflow. These ACE inhibitors are not only capable of reducing the afterload but can also reduce cardiac myocyte hypertrophy [68]. Numerous large-scale progressive study designs with a control group have demonstrated since the 1980s that an ACE inhibitor therapy lowers death rates in general, particularly in individuals who have cardiac failure and decreased ejection fraction (OHFrEF). These investigations reported that ACE inhibitors reduced fatality among individuals with failure of the left ventricle who are asymptomatic as well. These ACE inhibitors are greatly prescribed as the initial-choice treatment for individuals with cardiac failure according to the research findings [69].

7.5 Beta blockers

According to Do Vale et al. (2019), the main illnesses treated by beta-blockers as a group of therapeutic agents are coronary artery disease and other ailments [70]. Hypertension, migraine prophylaxis, glaucoma, portal hypertension, aortic dissection, essential tremor, hyperthyroidism, coronary artery disease, cardiac arrhythmias, congestive heart failure, myocardial infarction, and tachycardia have been recommended and approved to be treated with beta-blockers by the FDA [71].

7.6 Calcium channel blockers

Calcium channel blockers are agents with various pharmacological features and are most commonly applied in the area of CVDs to treat hypertension and angina pectoris, among various related conditions. In addition to their effects on arterial pressure and the smooth muscle of the coronary arteries, their ability to stabilize plaque is likely what mediates this protective impact [72]. Administration of calcium channel antagonists can be done orally or intravenously. A sign of efficacy would be the reduction of their angina symptoms or a steady rise in their blood pressure levels [73].

8. Conclusion

The onset of CVD is closely tied to apolipoprotein metabolic processes, and the roles of the many kinds of apolipoprotein are beginning to be understood. Clinical studies have frequently linked low levels of apo A-I and/or high levels of apo B to an elevated risk of cardiovascular events; the initial apo B level is a more reliable predictor of cardiovascular risk than LDL. When people are on lipid-modifying medications, apo A-I and apo B levels remain stable. Because apo A-I and apo B appear to have different effects on cardiac risk, the percentage difference between the two, which demonstrates a balance of atheroprotective cholesterol-rich vs possibly atherogenic components, may be a more significant risk predictor than either factor alone. Furthermore, assessing apolipoprotein levels is easy, does not require fasted blood samples, and is easily automated and standardized. As a result, in addition to their increased incidence of occurrence, apo B and apo A-I may be more methodologically advantageous as CVD risk indicators than LDL and HDL. To effectively measure cardiac risk and track the impact of cholesterol-lowering medicine, it may be sufficient to test apo A-I/apo B and maybe also TG, rather than the lipid ratios, non-HDL, HDL, LDL, TG, and TC recommended by the NCEP ATP III guidelines. Undoubtedly, apolipoprotein profiling is a useful predictor of cardiac risk, providing information that could help clinicians make better patient-specific treatment decisions. Treatment plans must be assessed in terms of how they affect both defined lipoprotein measures and apolipoproteins. Apo A-I and apo B should be included in revised guidelines because they are important indicators of lipid-lowering and cardiac risk medications. Randomized cardiovascular outcome trials are required to offer

definitive evidence of causality and evaluate the therapeutic efficacy of novel, potent lipoprotein(a) reducing treatments.

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