Iraqi Journal of Pharmacy 23(1) (2026) 1-11

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage : https://iphr.uomosul.edu.iq/

Review Article:

PCSK9 Relationship with LDL and LDLR: A Promising Method for Treatment of Dyslipidemia

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Article Information

Article history:
Received on: 01 May 2025
Revised on: 17 June 2025
Accepted on: 27 June 2025
Published on: 01 March 2026

Keywords:
Dyslipidemia,
LDL,
LDLR,
PCSK9.

Abstract

Background: One of the most significant risk factors for cardiovascular (CV) disease is dyslipidemia, exacerbated atherosclerosis, and premature mortality due to heart attack. Lipid disorders have several etiologies, categorized into primary and secondary types. PCSK9 serves as a crucial target for treating hyperlipidemia, not only because of its recent identification or the novel biological insights it has offered, but also due to significant scientific progress that has rapidly led to effective therapeutic applications. Hepatic PCSK9 is a significant circulating protein that regulates the half-life of both the VLDLR and the LDLR. Inhibiting it is considered to be one of the most cutting-edge and technologically advanced new treatment techniques for successfully decreasing LDL cholesterol levels. Statins are the drug of choice for most cases, even though some patients do not respond to statins even with high doses. **Objective:** The major aim of this study is to highlight the role of PCSK9 in regulating LDL and LDLR and the effect of statins, along with PCSK9 inhibitors, on LDL and LDLR and lipid profile in general. **Method:** To find pertinent trials regarding PCSK9's relation to hyperlipidemia and statin therapy between 2000 and 2024, the search strategy used electronic databases such as PubMed, Web of Science, Springer, Google Scholar, and others. **Conclusion:** The main kinds of frequently administered lipid-lowering drugs have been shown to raise serum PCSK9 levels. These findings most likely explain why these medicines are not more successful in lowering LDL-C and indicate that research should be done to create novel drugs that lower LDL-C by either lowering or inhibiting PCSK9 or by not raising circulating PCSK9 levels.

1. Introduction

1.1 Dyslipidemia

This health condition characterized by abnormal blood lipid levels [high or raised levels of plasma total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG), as well as low levels of high-density lipoproteins (HDL)], is a significant risk factor for the cardiovascular disorders, exacerbated atherosclerosis, and premature mortality due to the heart attack, arising from extrinsic, intrinsic, or a combination of environmental and genetic predispositions (1,2). However, cardiometabolic syndrome (CMS) is characterized by metabolic dysfunctions, including dyslipidemia, insulin resistance, central obesity, hypertension, and impaired glucose tolerance (3). Individuals with CMS have a threefold heightened chance of heart attack or stroke and a twofold greater risk of mortality from coronary heart disease compared to those without the syndrome. Moreover, central adiposity is widely acknowledged as a critical determinant of heightened cardiometabolic risk (4).

1.2 Basic lipid metabolism

lipids in plasma are categorized into cholesterols, which serve as precursors for steroids, and triglycerides, composed of glycerol and fatty acids. Cholesterol is integral in the synthesis of various molecules, including vitamin D, and is utilized by several organs, such as the adrenal gland, to produce sex hormones and corticosteroids. While

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How to cite:
Alhafidh, N., N., Khalaf, M., M., Mustafa, N., G., (2026). PCSK9 Relationship with LDL and LDLR: A Promising Method for Treatment of Dyslipidemia. Iraqi J. Pharm. 23(1), 01-11.

DOI: **https://doi.org/10.33899/iraqij.p.2025.159687.1149**

in the liver, cholesterols are employed to generate bile acids and salts. Additionally, cholesterols contribute to the structural integrity of cell membranes. Triglycerides function as an energy source, being stored in adipose tissue (5). However, lipids are not found in their free form in the blood due to their watery nature; hence, the liver converts them into lipoproteins. Cholesterol and triglycerides are sequestered within the hydrophobic core of spherical lipoprotein particles, shielded from the aqueous plasma by apolipoproteins and surface phospholipids (6). Lipoproteins come in various sizes, shapes, densities, and relative lipid contents. They are all defined by apolipoproteins, which also serve as ligands for receptors, stabilize particles, and cofactors for processing and transporter molecules (7). Lipoproteins are chylomicrons (CM), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) (8,9).

In addition, the liver produces triglycerides and cholesterol esters, subsequently reintroducing them into the bloodstream for distribution to tissues as VLDL. These are then modified by lipoprotein lipase (LPL), an enzyme that facilitates the hydrolysis of triglycerides, ensuring that the correct amount of fatty acids is provided to the relevant tissues at the right time (10). Hepatic lipase then transforms these lipoproteins into LDL, which are subsequently retrieved by the LDL receptor (LDL-R) (6). Following esterification by lecithin cholesterol acyltransferase (LCAT), extra cholesterol is converted to HDL and removed from circulation through reverse transport, subsequently being utilized by hepatocytes (11). **Figure 1** shows schematically the lipoprotein metabolic pathway.

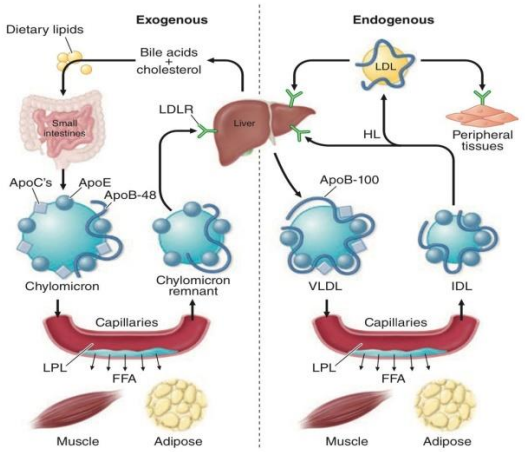

Figure 1. Exogenous and endogenous lipoprotein metabolism.

The exogenous pathway facilitates the transport of dietary lipids to peripheral tissues and the liver, while the endogenous pathway is responsible for the distribution of hepatic lipids to the periphery. Abbreviations include FFA (free fatty acid), HL (hepatic lipase), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), LDLR (low-density lipoprotein receptor), LPL (lipoprotein lipase), and VLDL (very-low-density lipoprotein).

1.3 Classification of dyslipidemia

lipid disorders have several etiologies, categorized into primary and secondary types. The initial group encompasses hereditary disorders, including familial chylomicronemia syndrome (FCS), autosomal recessive hypercholesterolemia (ARH), homozygous familial hypercholesterolemia (HFH), familial dysbetalipoproteinemia (FD), familial hypertriglyceridemia (FHTG), and others. Lipoproteins are the main transporters of lipids in the blood, and primary dyslipidemia results from problems with their production, distribution, or breakdown (12). Because these anomalies cause lipids and lipoproteins to build up in blood and tissues, they increase the risk of atherosclerosis and cardiovascular disease (13).

Nevertheless, illnesses influencing the function of certain organs, such as the kidneys, thyroid, and liver, fall within the second group (14). Hypercholesterolemia can result from hypothyroidism, nephrotic syndrome, cholestasis, anorexia nervosa, and certain medications, including progesterone, thiazide diuretics, carbamazepine, and cyclosporine (15). Conversely, hypertriglyceridemia may result from pregnancy, hepatitis, human immunodeficiency, obesity, type 2 diabetes, alcohol consumption, renal failure, sepsis, stress, Cushing's syndrome, viral infections, and certain medications (including thiazide diuretics, β-blockers, anabolic corticosteroids, estrogen, and protease inhibitors) (16). The following factors contribute to low levels of HDL cholesterol: β-blockers, steroids, smoking, obesity, type 2 diabetes, malnutrition, and lack of physical exercise. In addition, dyslipidemia can be exacerbated by unhealthy eating habits and lack of physical activity, particularly in younger individuals (17).

1.4 Consequences of dyslipidemia

Through a variety of pathways, dyslipidemia can result in inflammation, oxidative stress, cardiovascular disorders, and other metabolic dysfunctions.

1.4.1 Inflammation

Elevated levels of triglyceride-rich lipoproteins and LDL promote their accumulation in arterial walls, leading to inflammatory responses that facilitate the initiation and progression of atherosclerosis. The endothelium of blood vessels can be compromised by inflammatory mediators, such as cytokines and chemokines, along with activated inflammatory cells (including T cells and macrophages), resulting from dyslipidemia (18). Moreover, dyslipidemia increases the production of adhesion molecules such as vascular cell adhesion molecule-1(VCAM-1) and intercellular adhesion molecule-1(ICAM-1), inflammatory cells may connect and migrate more easily into the subendothelial region, which promotes a cascade of events such as activation of inflammatory pathways, calcification, ultimately hardening and narrowing of arteries (19,20).

1.4.2 Oxidative stress

LDL particles retained in arterial walls undergo oxidation. Oxidized LDL becomes pro-atherogenic and pro-inflammatory. This can elevate the production of unstable chemicals known as reactive oxygen species (ROS), which

oxidize proteins, lipids, and DNA. Although antioxidants can counteract ROS and shield cells and tissues from oxidative damage, they can also be reduced by dyslipidemia (21).

1.4.3 Cardiovascular diseases

By affecting the synthesis and availability of nitric oxide, a crucial regulator of vascular tone, blood pressure, and platelet aggregation, dyslipidemia can also have an impact on the heart's and the blood vessels' optimal function. Additionally, the effects of dyslipidemia on the structure and function of the heart muscle can lead to cardiac hypertrophy, fibrosis, and arrhythmias (22).

1.4.4 Additional metabolic issues

Alterations in lipid and glucose metabolism, insulin sensitivity, and inflammatory status significantly influence the metabolic processes of several organs and systems, including the liver, pancreas, adipose tissue, and skeletal muscle (23).

2. Treatment of dyslipidemia

The earlier European Society of Cardiology/European Atherosclerosis Society ESC/EAS lipid guidelines were released in August 2016 (24). In recent years, a significant amount of evidence has emerged, necessitating the development of new, updated guidelines. Atherogenesis begins with the preservation of LDL and other cholesterol-rich lipoproteins within the artery wall, as shown in the findings (25). Studies have demonstrated that atherosclerotic plaque and subsequent cardiovascular events are significantly influenced by LDL and other lipoproteins that are rich in cholesterol (26).

Consequently, the "LDL hypothesis" is no longer relevant; it is now firmly established that elevated LDL levels are causally associated with atherosclerotic cardiovascular disease (ASCVD), and that minimizing LDL particles and other lipoproteins (including ApoB) to the greatest extent possible reduces the occurrence of cardiovascular events (27) .

The ESC/EAS task force members who drafted these guidelines have updated the CV risk categorization and proposed new LDL objectives to reflect these latest findings. These changes are particularly pertinent to patients who are at high and very high risk (28). Despite lipid-lowering therapy (LLT), patients with elevated LDL levels do not achieve the LDL targets recommended by the ESC, and there are currently no established guidelines for screening adults with dyslipidemia. Screening for risk factors is advised to begin at a minimum age of 40 years (29). Regardless of gender, lipid profiles should be checked for anyone over 40 or those with risk factors, according to the Canadian Cardiovascular Society's (CCS) recommendations (30). However, some suggestions conclude starting to monitor lipid profiles around the age of 20. Men in this condition should retest between the ages of 25 and 30, and women, especially those in the high-risk category, should retest between the ages of 30 and 35 (31)Medication therapy is a crucial supplement to dietary changes for reducing LDL levels. Drug therapy usually has an effect more quickly than food therapy (32).

If one medication fails to lower LDL, it is advisable to consider additional pharmacological therapy. It is crucial to recognize that different lipid-lowering drugs can have a variety of adverse effects. Thus, the initiation of drug therapy is determined by factors such as age, severity of dyslipidemia, comorbidities, and the presence of other personal or familial cardiovascular disease risk factors. Pharmaceutical options should be selected based on a risk-benefit analysis, lipid profile, and the aforementioned factors. The classes of medications approved for treating dyslipidemia can be summarized as follows: Statins diminish intracellular cholesterol levels and promote LDL clearance by inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme-A(HMG-CoA), an enzyme that controls endogenous cholesterol production (33).

Pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin, and fluvastatin are the six main statin medications that are currently available in the local markets. It has been proven that therapy with statins is effective in lowering triglyceride levels by 10–20%, lowering levels of low-density lipoprotein cholesterol (LDL) by 20–50%, and perhaps increasing levels of high-density lipoprotein cholesterol (HDL) in the blood by 5–10% (34). When used in conjunction with statin medicine, ezetimibe can reduce the incidence of non-fatal strokes and heart attacks in high-risk individuals by increasing the medication's efficacy (35). The guidelines for the 2021 CCS dyslipidemia advocate utilizing it as a secondary therapy in addition to statin medicine to decrease cardiovascular risk in both primary and secondary prevention. This highlights the significance of its role in reducing the mortality rate associated with cardiovascular disease (36).

Ezetimibe is the primary option for combination therapy with the greatest tolerable dosage of statins if the LDL objective is not achieved. Ezetimibe functions by inhibiting the intestinal absorption of cholesterol, with its effectiveness contingent upon the blockade of the Niemann-Pick C1-like (NPC1L1) protein located in gastrointestinal epithelial cells (12). Bile acids are bound by bile acid scavengers, such as cholestyramine, colestipol, and colesevelam. This inhibits the absorption of bile acids and decreases their reuse, and increases the synthesis of bile acids in the liver, which in turn reduces the cholesterol level of hepatocytes throughout the metabolic process (37). They may be utilized with statins, as monotherapy, and in children over six years of age; however, their usage is not recommended for triglyceride levels over 500 mg/dL; instead, it should be cautiously administered for TG levels greater than 250 mg/ dl. They limit the absorption of fat-soluble vitamins and some drugs, and they are less effective than statins; therefore, they are rarely used. Some people also experience unpleasant side effects, including diarrhea and gastrointestinal upset (38).

On the other hand, fibrates promote the breakdown of TG and VLDL and act as agonists of nuclear peroxisome proliferator-activated receptor-α (PPAR-α) (39). They are recommended for patients with hypertriglyceridemia of >500 mg/dl or at the risk of pancreatitis who are not responding to dietary interventions. They are preferred in cases of hypertriglyceridemia, but their use in children under the age of 18 is not yet authorized. (40)Additionally, when used with statins, they have the potential to increase the risk of myopathy and rhabdomyolysis (41). Niacin brings down LDL by increasing HDL and decreasing VLDL; however, it comes with a significant list of side effects. This side effect is less likely to occur when using aspirin (38).

The innovative medication inclisiran, administered biannually, functions as an interfering ribonucleic acid that effectively inhibits the synthesis of PCSK9. Individuals who exhibit intolerance to LDL-lowering medications derive significant advantages from this therapeutic approach (42). Bempedoic acid serves as an alternative treatment option for patients who exhibit intolerance to statins, particularly when used alongside ezetimibe. This medication reduces cholesterol levels by inhibiting adenosine triphosphate citrate lyase, which increases cholesterol in the liver (43). Mipomersen, evolocumab, alirocumab, and evinacumab are some of the novel lipid-lowering drugs that have recently been reported in studies (2).

3. Screening tests

Most recommendations center on using a traditional lipid profile as a screening tool. TC, non-HDL, LDL, and TGs are included in this group (28,31). All recommendations advocate for the use of the non-fasting plasma lipid profile for screening within the general population, with LDL level evaluations serving as the primary method of lipid analysis. However, in populations exhibiting heightened triglyceride (TG) levels, non-fasting evaluations of LDL levels may yield inaccuracies. Consequently, for individuals with elevated TG levels, it is recommended to conduct fasting or direct measurements of LDL, especially for patients diagnosed with metabolic syndrome, diabetes mellitus, or familial hypertriglyceridemia (30). Some guidelines suggest evaluating ApoB-100 in addition to the normal lipid profile, as it accounts for all lipoproteins that are believed to be atherogenic (11).

4. Proprotein convertase subtilisin/kexin type 9 (PCSK9)

PCSK9 is an important target for treating hyperlipidemia, and not just because it was recently found or because it gave us new biological information. It's because big scientific advances have quickly led to beneficial therapeutic interventions (44). Even though there are over 560 proteases in humans, they may be categorized into five groups based on their catalytic action: peptidases that target serine, cysteine, aspartate, metallo, and threonine (45).

Proteases control a wide variety of important physiological processes, such as the immune response, cell cycle, apoptosis, wound healing, nutrient processing, and recycling of proteins and organelles (46). They function under strict supervision, and anomalies in their activity have been related to a variety of ailments, including cancer, inflammation, cardiovascular disease, and neurodegenerative disorders (47).

Proprotein convertases represent a small family of serine endoproteases, which are instrumental in regulating the balance of protein substrates within cellular environments. PC1/3, PC2, PC4, PACE4, PC5/6, PC7, Furin, SKI-1/S1P, and PCSK9 are the nine members of the PCs family (44). As furin and PACE4 play a part in viral infection, rheumatic diseases, cancer, and its metastases, they are attractive therapeutic targets. PC7 is associated with nervousness, PC4 with reproduction, and PC1 with obesity and type 2 diabetes (48).

Even though SKI-1 plays fundamental functions in regulating the creation of lipids and steroids, it is also responsible for increasing the infectiousness of viruses. This suggests that temporarily inhibiting its activity with medications may be beneficial (49). Hepatic PCSK9 is an important circulating protein that modulates the half-life of both VLDLR and LDLR. This protein is predominantly located in the liver. Inhibition of this mechanism is regarded as a leading-edge treatment approach for effectively reducing LDL cholesterol levels (44).

4.1 PCSK9's General Structure

PCSK9 was first identified as neural apoptosis-regulated convertase-1 (NARC1), the accomplishment of which was achieved by increasing the number of mRNAs that were capable of encoding an equivalent of SKI-1/S1P. Original research has identified PCSK9 in studies focused on apoptosis in cerebellar neural cells and secretory proteins. Subsequently, the cDNA of PCSK9 was discovered in libraries (50). The endoplasmic reticulum (ER) synthesizes PCSK9 as a 73 kDa zymogen, which undergoes modifications during transport to the cell surface. (51). The crystal structure reveals that PCSK9 features a distinctive C-terminal domain, known as the V domain, alongside pro- and catalytic domains that exhibit similarities to subtilisin (52), as shown in **Figure 2**.

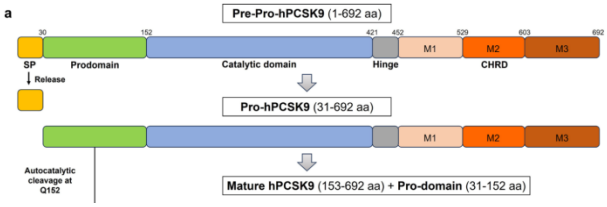

Figure 2. The primary structure and function of PCSK9. PCSK9 consists of a signal peptide (SP, amino acids 1–30), a prodomain (amino acids 31–152), a catalytic domain (amino acids 153–421) featuring a hinge (amino acids 422–452), and a Cysteine-Histidine rich C-terminal domain (CHRD, amino acids 453–692), which can be further categorized into three modules: M1 (amino acids 453–529), M2 (amino acids 530–603), and M3 (amino acids 604–692). In the endoplasmic reticulum, proPCSK9 experiences autocatalytic cleavage at the glutamine residue Q152. The prodomain is subsequently detached from the mature PCSK9; however, it continues to connect with the catalytic domain, therefore limiting the proteolytic activity of the adult PCSK9. (44)

Even though the entire PCSK9 (31–692) was employed for crystallization, only residues 61–683 exhibited electron density. The prodomain is found between residues 31 and 152. The catalytic domain contains two loops that lack electron density, extending from residues 153 to 421, from residues 453 to 692. The V domain has two disordered areas (**Figure 3**). The prodomain of subtilisin and the core of PCSK9 exhibit notable similarity, including four strands of an antiparallel beta sheet and two alpha helices (53). With 12 exons and 3,710 base pairs (bp) in length, the human PCSK9 mRNA codes for a 692 aa protein (44).

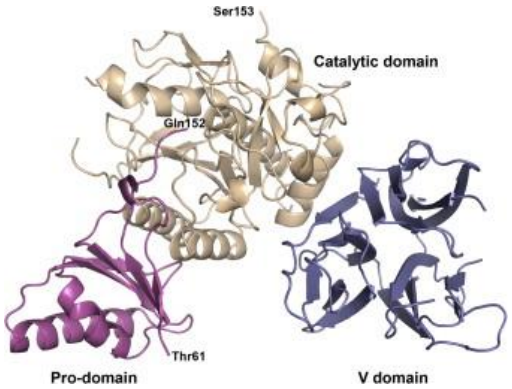

Figure 3. Overall structure of PCSK9 protein (53).

Prohormone-proprotein convertases are generated as zymogens after undergoing a multi-step maturation process, in this process, the prodomain first acts as an aid, essential to the proper folding of the catalytic domain, and then, when the catalytic domain has been folded, autocatalysis occurs between the prodomain and catalytic domain, Following the initial cleavage process, the prodomain remains associated with the catalytic domain, thereby inhibiting its catalytic activity. As development progresses under optimal conditions, a second autocatalytic event takes place within the prodomain (54,55).

The separation of the prodomain and the catalytic domain that occurs during this second cleavage event results in the production of an active protease. The PCSK9 zymogen undergoes autocatalysis between Gln152 and Ser153 (VFAQjSIP), and has been demonstrated to be necessary for its cell secretion (53,56). In the bloodstream, proprotein convertase subtilisin kexin type 9 (PCSK9) is recognized as a significant regulator of low-density lipoprotein (LDL) levels (44). The protease PCSK9 is primarily produced and secreted into plasma by the liver; however, it also comes, in lower amounts, from the kidneys, lungs, pancreas, small intestine, and central nervous system. It binds to and degrades hepatic LDL receptors (50).

However, LDL receptors (LDLRs) are essential for regulating blood levels of LDL cholesterol. Upon binding to LDL, LDLRs internalize the resulting complexes into clathrin-coated vesicles, which subsequently merge with endosomes through endocytosis. The acidic environment within the endosomes facilitates the dissociation of LDL particles, which are then transported to lysosomes for degradation into lipids and amino acids. LDLRs can be recycled back to the hepatocyte surface to facilitate the continued removal of LDL from the bloodstream. PCSK9 induces a conformational change in LDLR, inhibiting its recycling to the cell surface from the endosome. In contrast, for degradation, the PCSK9-LDLR-LDL-C complex translocates to the lysosome, where PCSK9 elevates serum LDL by promoting LDLR degradation, hence reducing LDLR levels on the cell surface (**Figure 4**)(44).

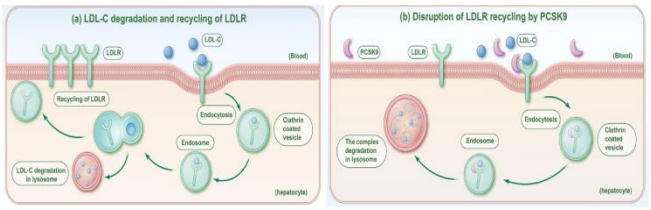

Figure 4. LDLRs play a vital role in regulating blood LDL cholesterol levels by managing their clearance from circulation. LDLRs bind to LDL-C, which is then endocytosed into clathrin-coated vesicles in hepatocytes. The endosomes' acidic environment dissociates the LDL-C particles, which are then transported to lysosomes for degradation into lipids and amino acids. LDLRs can recycle back to the surface of the hepatocytes to transport and clear additional LDL-C from circulation. (44).

On the other hand, the process by which PCSK9 destroys LDLR is far more complicated. According to the previous findings, PCSK9 does not need to engage in enzymatic activity to destroy the LDLR. This occurs after the process of self-cleavage and secretion has completed (57). Instead, PCSK9 attaches itself to the LDLR and then targets it for hepatocyte lysosomal degradation. The idea that PCSK9 lowers hepatic LDL levels is corroborated by many studies showing that employing an antiPCSK9 antibody to prevent PCSK9 from binding to the LDLR preserves LDLR and lowers LDL (58,59).

Numerous unique mutations of PCSK9 have been identified in individuals. Patients with a gain-of-function mutation in PCSK9 exhibit severe familial hypercholesterolemia, which is linked to an increased cardiovascular risk, however, lower blood LDL levels and cardiovascular hazard are observed in individuals with mutations that cause PCSK9 to lose its activity [loss of function- (LOF)], such as those that prevent the protein from self-cleaving and secreting (57). Three PCSK9 LOF variations—R215H, F216L, and R218S—have been identified within the enzymatic domain. The findings indicate that furin is capable of cleaving PCSK9 at RFHR218, thereby inactivating it (50). The D374Y variation is the most potent of all PCSK9 GOF variants (44). Resistant to furin cleavage and exhibiting an LDLR-binding affinity that is ten to twenty times greater (60–62).

There may be a third gene for familial hypercholesterolemia (FH) in addition to the now-known LDLR and Apo-B genes, because PCSK9 is located on the short arm of chromosome 1p32, near the 1p34.1p32 area that has been found and identified in big French families (50). The increased hepatic function to secrete cholesterol was associated with the specific 1p34.1p32 gene, which is connected to very low-density lipoprotein (VLDL), which transforms into LDL cholesterol following secretion (44,63). More extensive genetic testing, which included 23 French families without LDLR or Apo-B mutations, led to the discovery of two PCSK9 variations, S127R and F216L (50).

These findings shed light on the hereditary components of hypercholesterolemia and demonstrate that PCSK9 in humans is an important FH gene for LDL regulation (44). Consequently, in the context of the autocatalytic cleavage of its prodomain within the endoplasmic reticulum, PCSK9 operates solely as a protease, suggesting that the secreted form of PCSK9 modulates LDL levels via a nonenzymatic mechanism. This explains the presence of GOF variations, which are unusual for an enzyme (52,64). Numerous studies have linked PCSK9-GOF mutations to a heightened prevalence of coronary artery disease (CAD) and elevated cholesterol levels. In contrast, hypocholesterolemia and a decreased risk of developing coronary artery disease were linked to LOF mutations. Suggesting that individuals can lead normal lives despite the non-functional expression of PCSK9. Moreover, heterozygous complete PCSK9 loss-of-function mutations mostly protect individuals from coronary heart disease (CHD) and cardiovascular events throughout their lifespan (44).

At neutral pH, the kinetics of PCSK9 binding to cell-surface LDLR exhibit Kd values. (The dissociation constant (Kd) is an equilibrium constant employed in biochemistry and pharmacology to denote the binding affinity of drugs (66), ranging from 90 to 840 nmol/L. At lower pH, the attraction for the LDLR increases by two orders of magnitude, with Kd values between 1 and 8 nmol/L (53,60,67). The PCSK9–LDLR complex is targeted to the lysosome for degradation due to increased affinity at acidic pH, facilitating PCSK9's binding to LDLR in the late endosome. PCSK9 interacts with LDLR through a two-step process (68).

Rapid-phase binding, which accounts for one-third of all equilibrium binding, is differentiated by a half-time dissociation of twenty minutes and a binding half-time that ranges from five to ten minutes (69). In addition, low-phase binding, constituting two-thirds of all equilibrium binding, is characterized by a half-time dissociation of approximately 5 hours and a binding half-time of roughly 1.5 hours. Even during the processes of lysosomal shuttling, internalization, and the binding of PCSK9 to LDLR, these events occur two to three hours following the initial interaction (70).

In vitro, PCSK9-mediated LDLR degradation only becomes noticeable 12 to 24 hours after PCSK9 is added to cultivated cells. After internalization by LDLR, PCSK9 in mice stays intact in the liver for at least four hours. In humans, therapeutic PCSK9 inhibition only considerably lowers LDL levels two to three days after therapy begins (71,72). These findings make it abundantly evident that the initial PCSK9 interaction with the LDLR and the subsequent loss of LDLR occur at different times. When thinking about this seeming contradiction, there are several options to take into account (44).

Initially, the PCSK9–LDLR connection could need other events and interactions before both proteins are immediately shuttled to the lysosome for destruction (71). On the other hand, intracellular LDLR concentrations could be significantly higher than the density of LDLR on the cell surface, thus, PCSK9's initial removal of cell-surface LDLR is quickly restored until intracellular reserves are likewise exhausted (70). As previously stated, PCSK9 is primarily produced in the liver, with smaller units found in the kidneys, lungs, pancreas, small intestine, and central nervous system. With natural circumstances, PCSK9 is present in human smooth muscle cells (SMCs), but in monocytes, macrophages, and human umbilical vein endothelial cells (HUVECs), it is not. Nevertheless, under inflammatory conditions caused by lipopolysaccharide (LPS), HUVECs may produce larger quantities of PCSK9 (44). Hepatocyte nuclear factor 1α (HNF1α), Sirtuin 6 (SIRT6), forkhead box O3 (FOXO3), and sterol regulatory element-binding protein 2 (SREBP2) serve as the primary transcriptional regulators of PCSK9 expression (73).

When the PCSK9 gene was sequenced, a sterol regulatory element (SRE) site was revealed in the proximal region of the PCSK9 promoter (74). Some individuals with atherosclerotic cardiovascular disease (ASCVD) may exhibit inadequate responses to statin therapy due to the activation of upstream SREBP2, which promotes the production of PCSK9 (75). On the other hand, SREBP1 is required for the transcription of PCSK9, which is stimulated by insulin. Coffee, on the other hand, has the potential to reduce the levels of PCSK9 and CVE while simultaneously increasing the quantity of Ca2+ in the hepatic endoplasmic reticulum. This, in turn, suppresses the rhythmic generation of SREBP2 (74,76).

Furthermore, it was shown that dietary cholesterol dramatically decreased PCSK9, whereas SREBP1a and SREBP2 greatly increased it, indicating that PCSK9 was a cholesterol-regulated gene. Later, it was proven that this crucial revelation recognized statins' potential to enhance PCSK9 transcription (77). Given that patients reacted favorably to statin therapy and that NARC-1 appeared to have a role in cholesterol metabolism, the mechanism behind some documented human mutations causing hypercholesterolemia may be explained by the fact that PCSK9 itself could efficiently degrade LDLR protein, even though statin treatment and cholesterol deficiency positively regulated both PCSK9 and LDLR mRNA levels. Consequently, PCSK9 GOF mutations led to increased PCSK9-induced LDLR degradation (51,75,77).

The predominant class of pharmaceuticals employed to reduce LDL levels, statins, has been shown to augment the activity and nuclear translocation of SREBP-2, a gene-activating transcription factor for PCSK9 and LDLR (78). The findings regarding statin-induced elevations in PCSK9 elucidate the mechanism underlying the nonlinear dose-response relationship of statins, particularly if PCSK9 levels either continue to rise or plateau during statin therapy. Initially, PCSK9 levels may increase before subsequently decreasing, before reaching a new steady-state level of hepatocyte PCSK9 expression (57).

5. Lipid-Modifying Pharmaceutical Agents and PCSK9 Concentrations

5.1 Statins

Statins, which are sometimes referred to as HMG-CoA reductase inhibitors, are a class of LDL-lowering drugs that are administered the most frequently, even though they have several downsides. A limitation is that statin therapy does not provide a linear dose-dependent decrease in LDL (79). The expression of low-density lipoprotein receptor (LDLR) on the hepatocyte surface is stimulated by a reduction in intracellular cholesterol levels, resulting in enhanced clearance of LDL from the bloodstream and a diminished concentration of circulating LDL and other apo

B-containing lipoproteins, including triglyceride-rich particles (28). Long-term statin treatment has been associated with an increase in LDL levels, a phenomenon referred to as "statin escape" (24). Statins reduce hepatic intracellular cholesterol, leading to increased nuclear translocation of sterol-regulatory element binding protein-2 (SREBP-2). This process activates LDL receptor (LDLR) and PCSK9 gene expression, resulting in elevated circulating levels of PCSK9 (75).

As expected, statin treatment increases both PCSK9 and LDLR levels; rather than undergoing normal recycling, the enhanced PCSK9 binds to LDLR and directs it towards lysosomal degradation, thereby diminishing the efficacy of statin-induced LDL reduction (73). It was discovered in a study that lipophilic statins, which include atorvastatin, simvastatin, pitavastatin, and fluvastatin, were more effective in increasing PCSK9 than hydrophilic statins, which include pravastatin and rosuvastatin (79). Understanding the rapidity with which statins elevate PCSK9 levels and the duration of this effect is essential. The study concluded that high-dose atorvastatin significantly increased blood PCSK9 levels in a swift and sustained manner (80).

The PCSK9 gene might exhibit a more rapid, sensitive, or dose-dependent response to atorvastatin compared to the LDLR gene, even though atorvastatin has the potential to upregulate both genes through the activation of SREBP-2 (81). So, after being on statin medication for 12 weeks, we saw a pretty significant increase in plasma PCSK9 levels. But interestingly, that spike didn't stick around, and by the 52-week mark, those levels were lower (79). Moreover, the connection between PCSK9 and plasma LDL level is completely eradicated by statin medication, which restricts its potential application as a biomarker of lipid metabolism in the context of routine clinical practice (57,82). Therefore, it is essential to investigate whether baseline concentrations of PCSK9 in the bloodstream might predict the efficacy of statins in reducing LDL levels (30). Even though pitavastatin reduced LDL more than pravastatin, the quantity of PCSK9 increased was consistent between the two statins (83). Statins studies made some interesting findings that led to the idea that statins might do more than just lower LDL to have their clinical effects. This idea was later called "statin pleiotropy". To begin, the amount of heart disease that was prevented was a bit higher than what would be expected based on the fact that statins lower LDL.

Furthermore, in every significant research study, statins were repeatedly demonstrated to be successful in the main prevention of strokes (84). Initially, several possible pathways were put forward to explain statins' effects that seemed to be spread across multiple areas. One early idea was that statins fixed atherosclerotic plaque and lowered the number of clinical ischemic events by a large amount. As it became clearer that statin treatment helped stop and lessen plaque buildup, researchers turned their attention to vascular inflammation. When the cellular and humoral immune systems are overactive and reactive oxygen species production goes up, it can start a chain of events that make inflammation worse. These events include the release of cytokines and T lymphocytes, and the stimulation and recruitment of macrophages, which may make atherosclerosis and plaque more likely to happen faster. Several studies have demonstrated a correlation between the key inflammatory marker C-reactive protein (CRP) and heightened cardiovascular risk. Statins have been shown to reduce both short-term and long-term CRP levels by 14% (85).

5.2 Ezetimibe

Ezetimibe is another medicine that is frequently used to lower LDL levels. This substance efficiently blocks the uptake of both ingested and biliary cholesterol by binding to the cholesterol transport protein (86). Ezetimibe decreases hepatic cholesterol levels by limiting the amount of cholesterol the liver acquires from intestinal absorption. This increases hepatic LDLR expression, resulting in enhanced LDL absorption from the plasma and a reduction in circulating LDL levels (28). Both monotherapy with ezetimibe and combination therapy with statins resulted in a decrease of LDL cholesterol levels of around 21% and 23%, respectively (87).

In comparison to statins, the amount of research that has been published on the effects of ezetimibe (either on its own or in conjunction with statins) on PCSK9 levels is significantly lower. The administration of ezetimibe alone for seven months resulted in a significant increase of 37% in plasma PCSK9 levels in monkeys with dyslipidemia, according to a preclinical experiment (88). A significant increase in plasma PCSK9 levels was associated with statin medication in combination with ezetimibe, as compared to statin therapy alone (75).

5.3 Fibrates

They act as agonists of peroxisome proliferator-activated receptors-α (PPAR-α) via transcription factors that regulate various stages of lipid and lipoprotein metabolism, among other functions. Fibrates effectively reduce postprandial triglycerides, triglyceride-rich lipoprotein residual particles, and fasting triglyceride levels (28). Thus, fibrates raise high-density lipoprotein cholesterol levels by 5–15% and decrease plasma triglyceride levels by around 30–50% (89). The influence of fibrate medication on LDL and PCSK9 is not as pronounced as that observed with statin therapy; however, fibrate administration resulted in a reduction of PCSK9 protein expression and mRNA levels in hepatocytes (90). Fenofibrate (200 mg for 12 weeks) markedly raised the levels of PCSK9 in the blood by 25% (91).

5.4 Nicotinic acid

Nicotinic acid possesses a remarkable ability to enhance the overall plasma lipid profile by elevating HDL cholesterol levels while simultaneously reducing triglyceride, LDL cholesterol, and lipoprotein (a) levels (92). PCSK9 levels decreased by 13% following one year of treatment with a combination of simvastatin 20 mg and niacin, suggesting that niacin mitigates the statin-induced elevation in PCSK9 (79). Additionally, niacin reduced PCSK9 levels by 17% in individuals receiving fenofibrate and atorvastatin together (90).

6. Conclusion

Targeting PCSK9 has become a viable therapeutic approach for the treatment of hypercholesterolemia. Monoclonal antibodies and other PCSK9 inhibitors have been created to inhibit the interaction between PCSK9 and LDLR, decreasing LDLR degradation and increasing LDL-C

clearance. Clinical investigations have shown that these inhibitors can considerably lower LDL-C levels, providing an alternative or supplement to standard statin therapy. More information we have shown that one reason why higher doses of statins might not lower LDL-C proportionally could be because statins cause fast and long-lasting rises in PCSK9 protein levels. In adults undergoing maximally tolerated statin therapy or those who are statin-intolerant, ezetimibe and PCSK9 inhibitors may decrease the incidence of non-fatal myocardial infarctions.

6. References

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PCSK9وعلاقته بالمستقبلات الدهنية منخفضة الكثافة والمستقبلات الدهنية منخفضة الكثافة جدا

الخلاصة :من أهم عوامل الخطورة المتعلقة بامراض القلب والاوعية الدموية هي عسر دهون الدم لانها تساهم بتطور تصلب الشرايين والموت المبكر ويعود هذا السبب للازمة القلبية التي ممكن ان تسببها الدهون المتراكمة.مشاكل عسر شحوم الدم تقسم الى أولية (وراثية) و ثانوية (مكتسبة) مع وجود أسباب متعددة لكل نوع.من بين التطورات الحديثة للعلاجات ظهر البروتين PCSK9 كهدف علاجي جديد،و تعود هذه الاهمية ليس فقط لاكتشافه انما لانه غير و جدد مفهوم النظرية الجزيئية وممكن تحويل هذه الافكار الى علاجات سريرية فعالة. بروتينات PCSK9الكبدية تعتبر من البروتينات المهمة في الدورة الدموية وذلك لتاثيرها المباشر على عمر المستقبلات الدهنية منخفضة الكثافة و المستقبلات الدهنية منخفضة الكثافة جدا، وتثبيط عملها والتي تعتبر بدورها عامل مهم في السيطرة على وعلاج اضطرابات الدهون وعلى الرغم ان الستاتينات تعتبر العلاج المثالي لمعظم حالات اضطرابات الدهون الا انه بعض المرضى لايستجيبون لهكذا نوع من العلاج حتى مع الجرع العالية.**الهدف:**الهدف الاساسي من هذه الدراسة هي تسليط الضوء وتلخيص دور وعمل البروتين PCSK9في تنظيم مستويات البروتين الدهني منخفض الكثافة و مستقبلاته ,و تأثير الستاتينات مع مثبطات الPCSK9 على نفس البروتين ومستقبلاته وعلى ملف الدهن بشكل عام .**المنهجية:**تم جمع دراسات تربط اضطرابات الدهون و بروتين PCSK9 وعلاج الستاتين بين الاعوام 2000 و 2024وباستخدام قواعد البيانات PubMed, Web of Science, Springer, Google Scholar, وركز على ربط الراسات السريرية بالتجارب النظرية.**الاستنتاج:**معظم انواع العلاجات المستخدمة في اضطرابات الدهون اظهرت بانها ترفع مستوى البروتين PCSK9، وهذه الاستنتاجات توضح لنا عدم فعالية العلاجات بنسبة عالية في خفض الدهون والكوليسترول الدهني منخفض الكثافة، وتشير هذه النتائج الى ضرورة تطوير علاجات جديدة قادرة على خفض هذا النوع من الدهون من خلال تثبيط PCSK9 او منع زيادته في الدورة الدموية .

الكلمات افتتاحية: المستقبلات الدهنية منخفضة الكثافة و المستقبلات الدهنية منخفضة الكثافة جدا، PCSK9 ،عسر دهون الدم.