Journal of Diseases
2018 Vol. 5, No. 1, pp. 10-23
ISSN(e): 2410-6550
ISSN(p): 2413-838X
DOI: 10.18488/journal.99.2018.51.6.19

GENETIC INSIGHTS OF CHOLESTEROL AND ATHEROSCLEROSIS; COMPLEX BIOLOGY

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Article History
Received: 25 June 2018
Revised: 28 August 2018
Accepted: 3 September 2018
Published: 5 September 2018

Keywords
Atherosclerosis
Cholesterol
Apo-E gene
QTL
Reverse cholesterol transport
Cardiovascular diseases
C.pneumoniae

ABSTRACT

Atherosclerosis is multifaceted arterial disease involving collaboration of chromosomal and conservational factors; around seven million Americans are experiencing a heart attack during their lifetime. Many biomolecules play different roles in atherosclerosis such as 5-LO enzyme which play vital role in synthesis of leukotriene's inflammatory intermediates and proteins. Previous studies show that individuals suffering from coronary artery disease more commonly have C. pneumonia antibody than inhabitant's controls. In recent years the genes and genetic polymorphism which are associated with atherosclerosis had been identified. Phospholipid transfer protein will subsequently decrease the HDL mass and cholesterol efflux capacity due to its overexpression and deletation. Our aim of this review is to demonstrate complex biology of atherosclerosis and effect of cholesterol in cardiovascular diseases.

Contribution/Originality: This study is one of very few studies which have investigated for genetical treatment of atherosclerosis. This study uses new estimation methodology such as by inhibiting RCT. This contributes information about molecular genetic changes in atherosclerosis which open up new vista for further research work.

1. INTRODUCTION

Atherosclerosis generally occurs when the fatty, yellow-colored plaques i.e. (atheroma's) build up on the artery walls, narrowing the arteries and restricting the flow of blood [1]. It also known as arteriosclerosis, in which plaque of cholesterol is developed within walls of artery and result's in the restriction of blood flow. Further constricted artery circulation leads to less supply of oxygen to heart muscle, results in chest pain [2]. When cholesterol is passing through blood stream it converted into LDL (Low Density Lipoprotein) also name as 'Bad Cholesterol. If concentration of LDL Cholesterol is high, it can dramatically raise your risk of heart attack [3]. Plaque make arteries narrower, eventually leads to reduced or blocked blood flow. Some of the risk factor recognized in the development of atherosclerosis is hypertension, smoking, obesity, aging, dyslipidemia and diabetes. It involves both environmental and genetic risk factor. It is most common in developed countries such as Canada, atherosclerosis is leading cause of illness & death [4]. According to recent studies, one in five deaths in Canada is occurring due to atherosclerosis. Also in 7.1 million Americans experienced a heart attack during their

lifetime [5]. In recent studies suggest that by reducing the LDL-C Level to below that of current guideline target, further slowdown the atherogens and reduced the coronary event. Recent appreciation suggest that inflammatory response will contribute to the formation of atherosclerosis which implies that by inhibiting inflammation it may provide new anti-atherosclerosis therapy [6].

Atherosclerosis is multifaceted arterial disease involving collaboration of chromosomal and conservational factors. It is a condition in which plaque is generated amongst arteries [7]. Arteries convey oxygenated blood to heart and other parts of body. The tapering of arteries restricts the stream of oxygen rich blood [8]. It is principal origin of Coronary Heart Disease (CHD), Carotid Artery Disease (CAD) and peripheral arterial disease. Atherosclerosis may develop when some aspects destructs the interior layer of arteries [9]. These aspects may be smoking, elevated amounts of cholesterol and fats exist in blood, raised blood pressure, elevated amount of sugar present in the blood owing to resistance against insulin or diabetes. Atherosclerosis is not assigned to a gene [10]. More likely it is the inheritance of collective genetic factors alternatives in the appearance of Solitary Nucleotide. Most of our achievements in getting knowledge about the hereditary source of atherosclerosis have come from studies of "candidate genes," identified by biochemists and consequently scrutinized for genetic variations and associations in inhabitants [5, 11]. One of the best instances of a candidate gene is apolipoprotein E (ApoE) [12]. ApoE has been studied intensively a dominant player in plasma lipid metabolism, in which it the uptake of chylomicron and VLDL remnants by the LDL receptor and its colleague, LDL receptor-related protein(LRP) Common genetic differences (polymorphisms) of ApoE were acknowledged by Utermann and colleagues in the 1970s, and consequent studies by several laboratories discovered distinct relationship with plasma cholesterol levels and type III hyperlipidemia (and later, Alzheimer disease) [13]. The E4 allele (frequency 30%) produces high amount of cholesterol in plasma than E3 allele (population regularity 60%), while the E2 allele (frequency10%) reduces amount of cholesterol in plasma. In the US inhabitants, these mutual deviations of ApoE clarify 5% of the inherited variation in cholesterol levels [13, 14]. A remarkable example of a genetic collaboration is Type III hyperlipidemia. Nearly all individuals with this unique (1 thousand in several) hyperlipidemia are homozygous for the E2 allele, almost all human beings who are homozygous for the E2 allele do not possess the disorder [15]. Thus, to produce hyperlipidemia with homozygosis for the E2 allele other chromosomal and environmental factors are essential. Recent studies show that specific mutation in a laminA gene is cause of this disorder [16]. This gene terminates in an in-frame alternate splice transcript which codes a peptide comprising a 50–amino acid deletion in the carboxyl end [17]. The different disorders like dilated cardiomyopathy, familial partial lip dystrophy, and muscular dystrophy are result of mutation in the lamina A gene. While considering hundred out of thousands genetic differences, it has become possible to execute complete genome-association studies with the help of single-nucleotide polymorphisms in which polymorphism of 35 000 genes in the genome are interrogated for probable association with an intricate trait. Based on genome association studies on inhabitants in Japan, Ozaki et al concluded that the most considerable linked with MI arise with genetic mutations in the lymph toxin- (LTA) gene [18, 19]. While controlling immunoglobulin levels and in inflammatory response LTA plays a major role. a null mutation of the LTA gene in mice has a considerable effect on growing of atherosclerotic lesion which is shown by Schreyer and colleagues. Based on the findings with LTA, Furthermore Ozaki and colleagues investigated for proteins that relate to LTA, they presented that LTA secretion is regulated by galectin-2 using yeast2-hybrid system. Greater considerable connection is seen after testing for association between SNP of the galectin-2 gene and vulnerability to Myocardial Infarction. Pathway members can function as covariates in genetic studies is effectively explained by this analysis. Use of animal models, particularly the mouse used for identification of genes for common disease is another beneficial method [20]. Recently Mehrabian and colleagues recognized that 5-lipoxygenase (5-LO) plays a chief role in prone to atherosclerosis in mice. If susceptibility to CHD in population is also contributed by polymorphisms of this gene. An ordinary promoter polymorphism of the 5-LO gene related to carotid intimal-medial thickness.

5-LO is enzyme which plays a major role in the synthesis of leukotriene's, inflammatory intermediates obtained from the arachidonic acid oxidation. Enzymes may produce effect on the growth and survival of leukocytes in the vessel wall because enzymes show their activity mainly in leucocytes including monocyte-macrophages [19, 20]. In the leukotriene pathway, genetic changes in other genes such as 5-LO–activating protein, deliberate the risk of MyocardiaI Infraction and stroke in the Icelandic isolate is reported by workers at decode. They also presented that a distinct haplotype of 5-LO–activating protein is related to MI in patients in the United Kingdom. There are various infectious agents which affects atherosclerosis [11, 19]. ex C. pneumoniae. Various studies are carried out to study relation between infectious agent and atherosclerosis. To study a relation amongst C. pneumonia and atherosclerosis, two kinds of studies are done: seroepidemiologic and the illustration of the organism in atherosclerotic tissue. In 1988 Saikku et al. Showed that individuals having coronary artery disease (CAD) more commonly had C. pneumonia antibody than inhabitant's controls, this recommended that C.pneumoniae might be correlated with atherosclerosis [19]. Now seroepidemiologic studies have been established by many investigators nearby the world, and studies with same conclusions have been described. However, many well-performed studies get unsuccessful to invent the correlation. Elevated percentage of antibodies containing older adults and serological test limits the seroepidemiologic. While the most sensitive method of determining acute infection is C.pneumoniae MIF test, there is little proof that it can distinguish the persons having prior infection from those having chronic infection. Since almost everybody is infected with C. pneumonia during their lifespan and is regularly reinvested, the significance of the absence of antibody in 15–20% of older persons is not known. It could be communicated to the entire burden in the body, how newly a recrudescent infection has occurred, or to individual variation in an older person's immune response. In some persons C.pneumoniae has been in atherosclerotic tissue without antibody [21]. Greater accuracy cannot be expected from seroepidemiologic analysis due to this restriction. to increase the probability of a contributory relation of C. pneumonia with atherosclerosis is chief result of seroepidemiologic studies. For correlation of C. pneumonia and atherosclerosis, presence of C. pneumonia in athermanous plaques of coronary arteries and other vessels is strong evidence. Some structures which seems like unique pear shape on electron microscopy was discovered by Short, a South African pathologist furthermore that structures were described for C. pneumonia by Kuo. He presented these structures with the help of immunocytochemistry (ICC) with C. pneumonia–specific monoclonal antibody and with the polymerase chain reaction (PCR) which are revealed by Short for C. pneumonia [22]. With the help of numerous methods, further sequences of explorations are demonstrated C. pneumonia in coronary arteries as well as in other vessels which are responsible for developing atherosclerosis. Severe methods explain role of C.pneumoniae in atherosclerosis, this is concluded in near about forty-four publications. Three studies were unsuccessful to discover the microorganism [23]. Only PCR is used by these three. Total 18 isolations from coronary and carotid artery lesions were reported by five laboratories. over 50% of atherosclerotic tissue samples were give positive results for C. pneumonia are reported by laboratories with the help of ICC (with or without PCR) [11, 24]. For proving correlation between C.pneumoniae and atherosclerosis, various observational studies are presented more than researching. But Questions are arising related to the importance of the seroepidemiologic studies [24]. There is genuine question about how repeatedly C. pneumonia is found in atheroma. However, the frequent occurrence of the microorganism in atheroma arteries as well as in normal arteries is shown by several methods. Observational studies approve that pneumonia plays a role in the pathogenesis of atherosclerosis [12, 25-28].

1.1. Genetic Determination

In recent years the genes and genetic polymorphism which are associated with atherosclerosis have been identified [25-36]. The disease related to heart including monogenic disease in which the LDL level is elevated. Recent studies show that growing in identification of genetic risk factor involved in atherosclerosis [37]. In patient more than 600 mutations in LDLR gene have been identified due to depletion of LDL receptor [38]. For empathize

the molecular means of atherosclerosis two major approaches have been deliberate. First involved the Genome wide linkage studies have potential to find new genes involved in atherosclerosis by means of Quantitative Trait Loci (QTL) [39]. Secondly candidate gene approach can be used to cram the function of each particularized gene and it has been tested in association studies. Recent studies carried out into 19 humans related to atherosclerosis which results in two of them developed stroke linkage, six of them shows linkage to myocardial infarction, four for coronary disease, one shows linkage for acute coronary syndrome and one shows linkage for both Coronary artery disease and myocardial infarction. genes which involved in atherosclerosis can be analyses for their expression pattern and sequence, further verified in animal models and human studies [40].

Genome wide studies play a vital role in identification of gene in mice which affect the HDL Cholesterol level [41]. Also, these studies helpful in identification of genes involved in atherosclerosis by following ways, Firstly the genes confirmed related to narrow region and their function is determined, also in QTL associated region confined to candidate gene, and lastly for testing dense SNPs, some of QTL can be selected [42]. According to recent knowledge two diseases which affect the progression if atherosclerosis involves Dyslipidemia and Inflammatory response [43]. Recently two genes which identified in human studies related to myocardial infraction such as (ALOX5AP and MEF2A), also two genes involved in atherosclerosis in mice linkage studies are (ALOX5 and Tnfsf4) [44]. Genetic linkage studies helpful in finding of new genes for disease [45]. Mutation observed in disease provides the diagnosis of genetic disease, such as mutation in protein required for elimination of sterol results in Hypercholesteromia [46]. Mutation observed in ABCG5 gene is of two types Q16X and R446X. These both mutation confirmed by sanger sequencing observed in 10-year girl with Sitosterolemia [47].

Coronary artery disease generally influences men rather than women. Recent studied reconnoitered function of Y chromosome discrepancy in the sexual dimorphism [46, 47]. Various studies are carried on different haplogroup of the Y chromosome in numerous British men and found that conjoint haplogroup revealed that 50% age adjusted risk of coronary artery disease. For determination of location of gene in human disease related to chromosomal region genetic linkage analysis method is apply [37]. Detection of mutation in several disease varieties of scanning techniques is available. With the help of technique that is affected relative pair linkage responsible for identification of genomic regions using single gene [38]. Familial hypercholesterolemia identified by increase plasma cholesterol which meets LDL and forms complex LDL-C because of absence of LDLR activity at cell surfaced present on chromosome 19 on the 19p 13.1-p13.3 and code protein have 860 amino acids [48]. It involves more than 800 allelic variations &involves most common mutation like P.C152R, P.S265R, P.V408M and P.G528D [49]. However, the APOB Gene has located on chromosome 2 at 2p24-p23 [32]. The mutation observed in APOB gene results in familial hypobetalipoproteinemia and familial ligand defective Apo B - 100 disease. It also having more than 80 allelic variations in human gene observed [50]. APOE is important gene playing a vital role in lipid transporting and maintaining the serum cholesterol level in body. It mapped to chromosome 19 at 19q13.2 [51]. Mostly major three alleles were found in this gene such as APOE2, APOE3 and APOE4.

Another gene ABCA1 which important for transportation of cholesterol in body. The mutation in this gene results in Tangier disease and positioned on short arm of chromosome 9 at 9q31.1. CYP7A1 gene mapped to chromosome 8 at site 8q11-q12 [52]. Gene helps in conversion of cholesterol to bile acid [53]. Mutation observed in these gene results in Hypercholesterolemia. ABCG5 and ABCG8 are of ATP binding cassette of family G members. Mutation results in Sitosterolemia [54]. SCARB1 it is type of a scavenger receptor which located on chromosome 12 at 12q24.31 [55]. Allelic variation observed within the coding region between exon 1 and 8. SPP1 gene observed at site of calcification in atherosclerotic plaque and mapped at chromosome 4q21-q25 [56]. TNFRSF11B Gene having vital role in plaque instability in atherosclerosis disease which mainly located on chromosome 8q24 [57].

Table-1. Information related to responsible gene [58-60].

Gene	Location	Allelic variation	Mutation
LDLR	Chromosome 19 19p13.1-p13.2	800	P.C152R P.S265R P.V408M P.G528D
APOB	Chromosome 2 2p24-p23	<80	_
APOE	Chromosome 19 19q13.2	3 APOE2 APOE3 APOE4	_
ABCA1	Chromosome 9 9q31.1	_	_
CYP7A1	Chromosome 8 8q11-q12	_	_
ABCG5-ABCG8	2p21	_	_
SCARB1	Chromosome 12 at 12q24.31	8 allelic variation found within exon 1 and 8	_

Source: From Pubmed Database ncbi.nlm.nih.gov/gene/3949

However, this genetic factor exhibit role in predisposition to atherosclerosis disease and related to coronary artery disease (CAD). For fortitude of these complex trait and genetic risk the allelic associate on study are employed [61]. In this study, it assesses the alleles and its genotype for gene in individual which are pretentious and unpretentious by disease. For coronary artery disease the genes encompassed in lipoprotein synthesis, metabolism and modification will developed atherosclerosis [62]. Recently studies carried out in individuals will unearth a new genetic threat factor for CAD, HUMPONA (Human Paraoxonase/Arylesterase) the new gene will be developed the atherosclerosis. HUMPONA gene mapped to chromosome 7q21-22 and will code for protein of 355 amino acids. Another genetic risk factor for atherosclerosis is augment in blood level of total homocysteine (tHcy) will leads in coronary artery disease [61, 63]. Recently in MTHFR gene the 677CT Mutation was observed. Several studies were carried out for MTHFR 677CT Gene mutation leads to genetic risk factor for development of atherosclerosis. In mice either ApoE or LDLR will formed atherosclerotic lesion analogous to that of in humans [64].

Two defective alleles for lipoprotein lipase gene trailblazers to coronary artery disease, recent studies carried out will results in over 60 mutations observed in Lipoprotein lipase gene. Mutation observed in the genes such as LDLR1 and its ligand APOB2 will developed atherosclerosis [65]. In PCSK9 gene missense type of mutation also lead to Hypercholesteromia. According to Dallas Heart Study, in subject with low LDL Level due to mutation in PCSK9 gene determining whether loss-of-function will occur in body which directly linked with Hypercholesteromia [66]. Recent study carried in 64 African American subjects will contrast the by DNA sequencing two nonsense type of mutation observed at (426C-G) in exon 3 of PCSK9. According to NMR spectroscopy (Nuclear Magnetic Resonance) will indicate that size dispersal of LDL Particles in subject which having nonsense mutation [67]. Finally, overexpression of gene PCSK9 will leads to elevated plasma LDL Level.

Table-2. Composition for diagnosing the atherosclerosis

Gene name	Locus	Source
KR 1020150116131-A/5	LG069993 20 bp DNA linear	Synthetic construct
KR 1020150116131-A/4	LG069992 20 bp DNA linear	Synthetic construct
KR 1020150116131-A/3	LG069991 8035 bp DNA Linear	Synthetic construct
KR 1020160089001-A/8	LY264191 20 bp DNA Linear	Synthetic construct
KR 1020160089001-A/7	LY264190 20 bp DNA Linear	Synthetic construct
KR 1020160089001-A/6	LY264189 20 bp DNA Linear	Synthetic construct
KR 1020160089001-A/5	LY264188 20 bp DNA Linear	Synthetic construct
KR 1020160089001-A/4	LY264187 20 bp DNA Linear	Synthetic construct
KR 1020160089001-A/3	LY264186 20 bp DNA Linear	Synthetic construct
KR 1020160089001-A/2	LY264185 20 bp DNA Linear	Synthetic construct
KR 1020160089001-A/1	LY264184 20 bp DNA Linear	Synthetic construct

Source: PCR Sequencing from Pubmed database

Table-3. Genes express in the atherosclerosis

Gene name	Accession no	Score
Expression vector pBJS001	FJ756409.1	100%
Retroviral vector pLNCX	M28247.1	100%
Moloney murine leukemia virus retroviral vector pLHDCX	M64754.1	100%
Mammalian expression vector LNXCO4	LT727331.1	100%
Mammalian expression vector LNXCO3	LT727330.1	100%
Mammalian expression vector LNXRO2	LT727329.1	100%
Retroviral vector NIT	AF311318.1	100%

Source: From NCBI Pubmed gene database

1.2. Roles of Protein in Atherosclerosis

Phospholipid transfer protein will subsequently decrease the HDL mass and cholesterol efflux capacity due to its overexpression and deletation. Plasma phospholipid transfer protein (PLTP) alters adaptive immune function through modulation of T helper cell [68, 69]. Repress LPS induced inflammation is difficult due to binding capability of the PLTP [70]. Functional expression of PLTP effects on HDL subspecies [71].

1.3. Effect of Cholesterol

Cholesterol has a well-recognized role in the pathogenesis of atherosclerosis. It undergoes impulsive autoxidation, leading to the formation of oxidized derivative which is more injurious to arterial wall than cholesterol [72]. It is believed that the initial event in atherogenesis is injury to arterial endothelium follow by inflammatory response in the arterial wall [73]. Response includes raised turnover and permeability, intimal edema and infiltration of monocytes that ingest extra intimal lipids and transform into foam cells [74]. Lesion progression may have influenced by endothelial denudation and replication, not only by permitting platelet adhesion and lipid penetration, but also by production of substance promoting smooth muscle proliferation [5]. Cholesterol is fat like substance in the body [6]. It is generated by your body and unearthed in food .while it is obligatory for good health; extravagantly cholesterol can destruct your arteries and escalate your risk of heart disease [75]. It forms in liver and allocated to other parts of body for formation of hormone and cell membrane [76]. Current studies ascertained that ideal cholesterol level is below 150 mg/dl. However, as cholesterol is comes in blood stream get crowded into low density lipoprotein named as Bad cholesterol [77]. LDL subsequently risen the risk of CHD [78]. The center for disease control and prevention assembled data in 2005-08 that results in treatment of high LDL levels [79] . Nearly 71 million American adults having greater LDL Level, instead of them 31 million people received treatment. As cholesterol leaves the dead cells it is trapped up for throughout by HDL known as Good cholesterol [80, 81]. Glomset proposed the Reverse cholesterol transport is used as physiological process in which cholesterol in peripheral tissue transported by HDL towards the liver for removal of Bile or feces [82].

Apolipoprotein (a) gene used to control lipoprotein levels [83]. Apolipoprotein E gene used to control triglyceride and plasma cholesterol level [84]. To control triglyceride apolipoprotein A 5 gene use [85]. Metabolites of blood ascertaining to informative intermediate phenotype regard to CAD. Trimethylamine-N-oxide is strong metabolite accompanying with atherosclerosis in the inbred strain of mice and human population [86].

MAO is upholding the materialization of foam cells. However, establishment of TMAO is owing to enzymatic oxidation of trimethylamine, destruction of choline generates a gas in intestine due to activity of gut bacteria [87]. Lavin monooxygenase is the enzymes that transform TMA to TMAO.TMAO levels are indomitable by level of diet and also by the variation in composition of gut flora [88]. Nevertheless in addition to lipid uptake route of cholesterol efflux synchronized by PPARγ [89]. They provoke ABCA1 expression and cholesterol exclusion from macrophages across transcriptional cascade facilitated by the nuclear receptor LXRα.To maintain chronic inflammation within a wall of artery progresses atherosclerotic plaque which is originated by oxidized lipids The result of oxidative modification which is secured by LDL comprises capability to encourage specific changes in macrophage gene manifestation [90]. Current work has originated a pathway for cholesterol efflux by lipid low dead cells [91]. However, LXRα and PPARγ both are triggered by lipid modules of oxLDL assumed nuclear receptor consist of cascade synchronizes a macrophage response to oxLDL uptake [92]. Epidemiologic studies have steadily revealed that plasma concentration of HDL cholesterol and apolipoprotein A-1 are contrariwise with CHD [93, 94]. Clinical trial specify modest enhance in HDL cholesterol concentration ominously diminish risk of CHD [95]. On HDL-C has an unassertive consequence by 3 hydroxy-3 methyl glutaryl co-A Reductase inhibitors or statins induce them on average by 5-10 %.The increased HDL-C [96]. Are seldom >25%, by fibrates and niacin (cannot bear) [97].

1.5. Reverse Cholesterol Transport

For anticipation of atherosclerosis accumulated cholesterol is to be transported from vessel wall to the liver for excretion by the pathway called as Reverse cholesterol transport [98]. HDL, apoA-1 and enzymes for instance lecithin; cholesterol acyltransferase, phospholipids transfer protein, hepatic lipase and cholesterol ester transfer protein are the major constituents of RCT.cholesterol efflux is critical part of RCT [99]. Which include removal of accrue cholesterol from macrophages in the sub intima of vessel wall via ATP-binding membrane cassette transporter A1 or by passive diffusion [100]. Esterified cholesterol present in the HDL is transported to liver for excretion. Patients having mutated ABCA1 gene RCT and cholesterol efflux are prejudiced and atherosclerosis is increased [99, 101]. Interruption of ABCA1 gene can encourage atherosclerosis in studies beside transgenic mice. As the level of HDL increases the prevalence of CHD gets decreased [102]. Extension with High Density Lipoprotein or apolipoproteinA-1 can inverse ATH via hastening reverse cholesterol transport and cholesterol efflux [103]. Conferring in vitro studies of ATH pro-inflammatory factors as interferon-gamma, endotoxin, and tumor necrosis factor-alpha and interleukin-1 beta can be atherogenic via prejudicing reverse cholesterol transfer and cholesterol efflux [104]. Amendment in RCT and cholesterol efflux proved to be anti-athrogenesis and may provide new therapeutic approaches to CHD [105]. Broaden research on new modifying factors for RCT and cholesterol efflux is warranted [106].

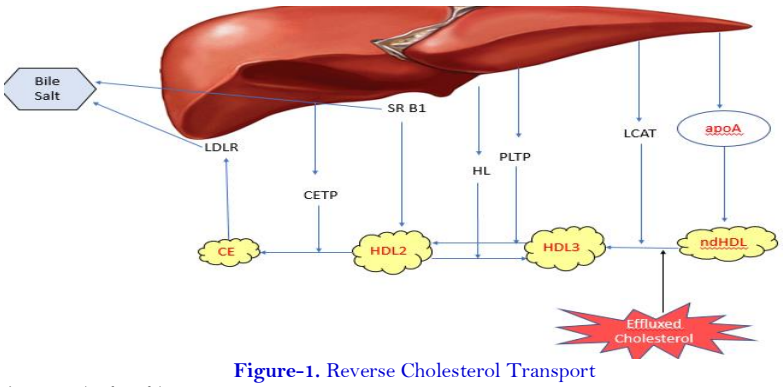

Figure-1. Reverse Cholesterol Transport

Source: From Siri-Tarino, 2011/ pubmed/21901431

Figure 1. Reverse cholesterol transport. The RCT pathway transports free cholesterol from macrophages or other cells to the liver or intestine for excretion. Main constituents of RCT comprise acceptors such as high-density lipoprotein (HDL) and apolipoprotein A-I (apoA-I), and enzymes lecithin: cholesterol acyl transferase (LCAT), phospholipids transfer protein (PLTP), hepatic lipase (HL) and cholesterol ester transfer protein (CETP), which control cholesterol transport. Ultimately, cholesterols in the HDL are delivered to the liver by scavenger receptor B1 (SR-B-1), converted to bile salts and excreted through the GIT. Cholesteryl esters (CE) could be delivered to the liver by the low-density-lipoprotein receptor (LDL-R). ndHDL, nascent discoidal high-density lipoprotein.

In fig.1 sequence of events in RCT is explained. ApoA -1 is formed mainly by the liver, and then release into plasma. apoA-1 reacts with serum phospholipids and forms ndHDL. Activation of cholesterol in macrophags and fibroblast absorb external cholesterol and generate Esterification by lecithin: cholesterol acyltransferase (LCAT).HDL particles are rich in cholesteryl ester and become larger, forming HDL3 and HDL2.phospholipid transfer protein act by fusing two HDL3 into one HDL2 molecule. Molecules are processed by the enzyme hepatic lipase and become smaller and denser.

If they are rich in triglycerides. HL can change phospholipids-rich HDL2 to HDL3.cholesterol ester transfer protein (CETP) assist the equimolar replacement of cholesteryl ester from HDL for triglycerides in apoB 100-containing lipoprotein. Cholesteryl esters are then transported back to liver by LDL-receptar.and convert to bile salts and eliminated through the GIT.

Cholesterol from extra hepatic cell and tissues is conveyed to the liver and intestine for excretion via RCT pathway [107]. RCT may counteract elaboration of ATH by means of lowering accumulation of cholesterol in wall of arteries [108]. CH efflux is major process via macrophages within a vessel wall emit cholesterol outside the cell [109]. The efficiency of RCT and CH efflux can be determined by HDL levels [110]. LDLR (Low density lipoprotein receptor) will play important role in preventing Hypercholesteromia and Atherosclerosis removing LDL from circulation [111]. (Increase HDL) Epidemiological studies reveal that there is antithetical correlation between level of HDL and risk of atherosclerosis [112]. Due to Obesity Ciggarate smoking, Male sex will ultimately decrease the HDL level. Recent study shows that CETP (Cholesteryl – Ester Transfer Protein) gene mutation was observed in four Japanese families with increase HDL level [113].

2. CONCLUSION AND DISCUSSION

Atherosclerosis is a complex disease depends upon its interaction between genotype and environment. In past few years for understanding the genetical basis of atherosclerosis genome wide linkage studies play important role. Since development of "next generation genomic sequencing technology" (NGS) we can be obtained a whole genomic sequence data for an individual. Our study aims at targeting the genes which associated with risk factor of atherosclerosis will ultimately results in diagnosing the atherosclerosis. Also, we provide some another risk factors which causes the atherosclerosis. In recent year development of some new technologies will help in contributing the unrevealing the complexibilities of these disorders such as for measurement of structural and functional changes in arterial wall the electron beam computed tomography and magnetic resonance imaging technology will precede the development of obstructive disease.

Funding: The authors are thankful to Riddhi Kamble and Principle, Gourishankar institute of pharmaceutical education and research limb, Satara [MS] India
Competing Interests: The authors declare that they have no competing interests.
Contributors/Acknowledgement: All authors are equally contributed.

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