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A comprehensive approach to the treatment of atherosclerosis by increased ApoA-I and HDL-cholesterol levels

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Abstract
In human body, cholesterol is transported around in the form of lipoprotein (lipid/protein) complexes, because it is almost insoluble in water. Extensive study shows that High-density lipoprotein (HDL) particles transport cholesterol from tissues back to the liver for excretion. Epidemiological studies have shown an inverse relationship between blood levels of HDL-cholesterol (HDL-c) and the incidence of clinically significant atherosclerosis. The beneficial effects of HDL in altering atherosclerotic disease are believed to involve elevated levels of HDL enhancing the efflux of cholesterol from arterial walls, increasing transport of cholesterol from arteries to the liver for excretion. This reverse cholesterol transport (RCT) pathway is used to explain both HDL's role in lipid metabolism and the inverse association between HDL-c plasma concentration and the risk of cardiovascular disease. Based on the RCT model, ApoA-I is an attractive target for therapeutic intervention. Experimental manipulations to increase production of ApoA-I have been associated with reduced atherogenicity. There is a continuing need for novel therapies that increase the biosynthesis of HDL, to inhibit the progression of and even bring about regression of atherosclerosis. Small molecule compounds that increase the production of endogenous ApoA-I would be attractive therapeutic agents for treating dyslipidemias.

Keywords: Cholesterol, apolipoprotein A-I (ApoA-I), high-density lipoprotein (HDL), reverse cholesterol transport (RCT), atherosclerosis, dyslipidemia

Introduction
Because of insoluble properties in water, cholesterol is almost transported around the body in the form of lipoprotein (lipid/protein) complexes [Fig-1].

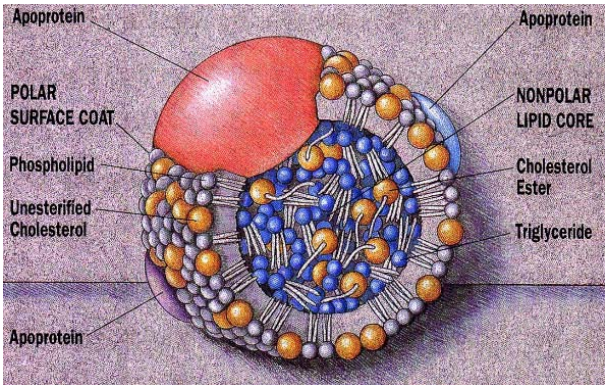

Fig 1: details about generic **li**poprotein.

The liver produces very low density lipoproteins (VLDL) and secretes them into plasma, where they are converted to low-density lipoprotein (LDL) particles and non-esterified fatty acids [1]. High-density lipoprotein (HDL) particles transport cholesterol from tissues back to the liver for excretion, as fecal sterols and bile acids. HDL exists primarily in two forms, one containing apolipoprotein A-I (ApoA-I) and apolipoprotein A-II (ApoA-II), and one containing ApoA-I alone [2]**.** The cardio-protective effect is largely due to ApoA-I.

In addition to their role in RCT, HDL particles comprises anti-inflammatory, anti-oxidative, anti-apoptotic, anti-thrombotic, vasodilatory, and antiinfective properties. Statistics of lipid metabolism also reveals that dyslipidemia is associated to atherosclerosis [3A, 3B, 3C, 3D, 3E]. The validity of the hypothesis was ultimately established by major epidemiological studies**,** such as the "Seven Countries Study," which, with a 25-year follow-up, found that across cultures, cholesterol levels were linearly related to coronary heart disease mortality [4]. Other epidemiological studies, including the Framingham and Procam studies, and it has also found that, there isan inverse relationship between blood levels of HDL-c and the incidence of clinically significant atherosclerosis [5]. This inverse association between HDL-c concentrations and cardiovascular risk is apparently continuous; there seems to be no threshold value.In fact, each 1 mg/dL increment in serum HDL-c is associated with a 2%–3% decrement in cardiovascular risk, while a 1% reduction in LDL-c decreased the risk of coronary heart disease (CHD) by 1%–2% [6]. The Veterans Affairs HDL-c Intervention Trial (VA-HIT) examined the benefit of secondary prevention in patients with low HDL-c levels and a history of coronary artery disease (CAD).

Apolipoprotein B is the primary apolipoprotein of chylomicrons, VLDL, IDL, and LDL particles (LDL - known commonly by the misnomer "bad cholesterol" when in reference to both heart disease and vascular disease in general), which is responsible for carrying fat molecules (lipids), including cholesterol, around the body (within the water outside cells) to all cells within all tissues. While all the functional roles of ApoB within the LDL (and all larger) particles remains somewhat unclear, it is the primary organizing protein (of the entire complex shell enclosing/carrying fat molecules within) component of the particles and is absolutely required for the formation of these particles. What is also clear is that the ApoB on the LDL particle acts as a ligand for LDL receptors in various cells throughout the body.

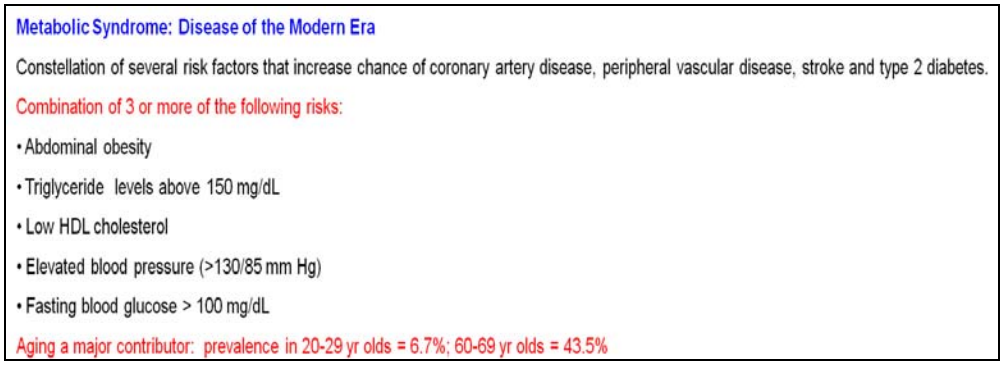

Fig2: *demonstrates several risk factors associated with CAD*

In patients with existing CAD, the only lipid abnormality seemsa low HDL-c level.The INTERHEART study, an international case control study comparing myocardial infarction survivors with age-and gender-matched controls, showed the ApoA-I/Apo-B ratio to be the strongest modifiable protective factor [7].

Reverse Cholesterol Transport (RCT)

The process whereby excess cholesterol in peripheral cells, especially foam cells, is returned to the liver for degradation and excretion.

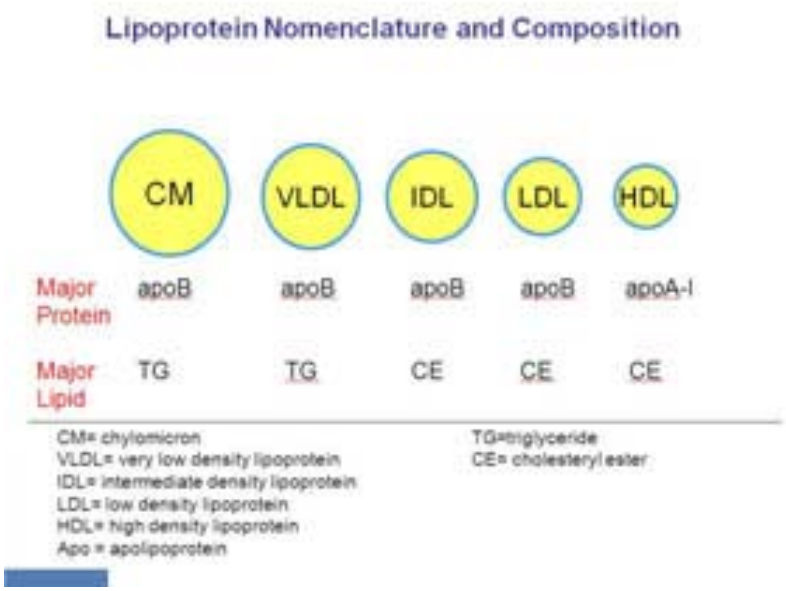

Fig 3: demonstration about the different sates of Lipoproteins.

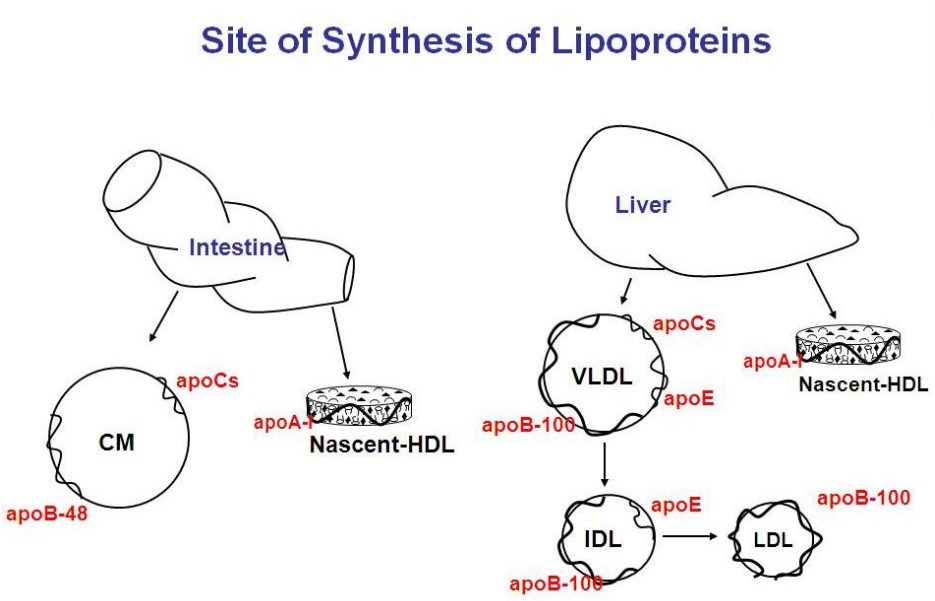

Fig 4: demonstrates about the site of synthesis of Lipoproteins.

Major Apolipoproteins and Their Function

Apo	Lipo	Origin	Function
ApoA-I	HDL	Liver, intestine	Activate LCAT, Cholesterol efflux via ABCA1 transporter
ApoB-100	VLDL, LDL	Liver	Ligand LDL receptor, TG transport from cells
Apo(a)	Lp(a)	Liver	Inhibits fibrinolysis
ApoCII	HDL, VLDL	Liver	Activates lipoprotein lipase
ApoE	VLDL, IDL	Liver, intestine	Ligand, LDL receptor, LRP receptor

LCAT: lecithin:cholesterol acyltransferase
ABCA1: ATP binding cassette protein A1
LRP: LDL receptor related protein

Fig 5: Major Apolipoproteins and their functions

RCT involves apoA-I [Fig:5], ABCA1 and LCAT as well as Receptors on the liver for uptak**e** of the excess cholesterol**.** While the mechanisms of the beneficial effects of HDL in altering atherosclerotic disease are not completely understood, it is believed that elevated levels of HDL enhance the efflux of cholesterol from arterial walls, increasing transport of cholesterol from arteries to the liver for excretion. Elevation of ApoA-I increases *paraoxonase* activity, and enhances anticoagulant and anti-inflammatory activities. HDL also promotes fibrinolysis.Additionally, HDL particles protect against LDL oxidation, plays a key step in promoting cholesterol uptake by arterial macrophages. The major steps in the reverse cholesterol transport (RCT) pathway [Fig:6] are the active efflux of cholesterol and phospholipids from cells by ATP-binding cassette transporter A1 (ABCA1), the binding of cholesterol to apolipoproteins, forming pre-HDL, the esterification of HDL-bound cholesterol by lecithin cholesterol acyl - transferase (LCAT;the resulting cholesteryl esters (CEs) are the core lipids of HDL)[Fig:7], CETP-mediated exchange of CEs andTGs between HDL and Apo B-containing particles,and hepatic lipase (HL)-mediated uptake of cholesterol and TGs by the liver. This RCT conceptis used to explain both HDL's role in lipid metabolism and the

inverse association between HDL-c plasma concentrations and cardiovascular disease risk. The effects of mutations in the various proteins and enzymes of the RCT pathway have helped in our understanding of cholesterol metabolism. Based on the RCT model, ApoA-I is an attractive target for therapeutic intervention. Experimental manipulations that increase production of ApoA-I have been associated with reduced atherogenicity. Human ApoA-I is protective in transgenic animal models[8A, 8B, 8C, 8D]and infusion of ApoA-I prevents atherosclerotic lesions and leads to regression of atherosclerotic plaques in human patients. Small-molecule compounds that increase the production of endogenous ApoA-I would be attractive therapeutic agents for treating dyslipidemias.

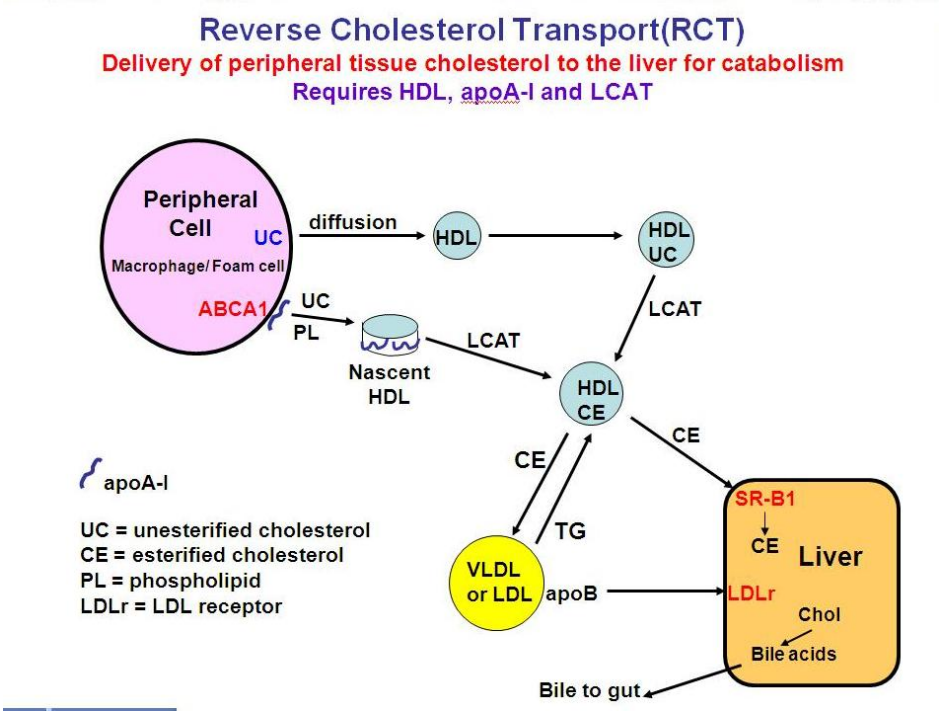

Fig 6: demonstrates details about Reverse Cholesterol Transport System

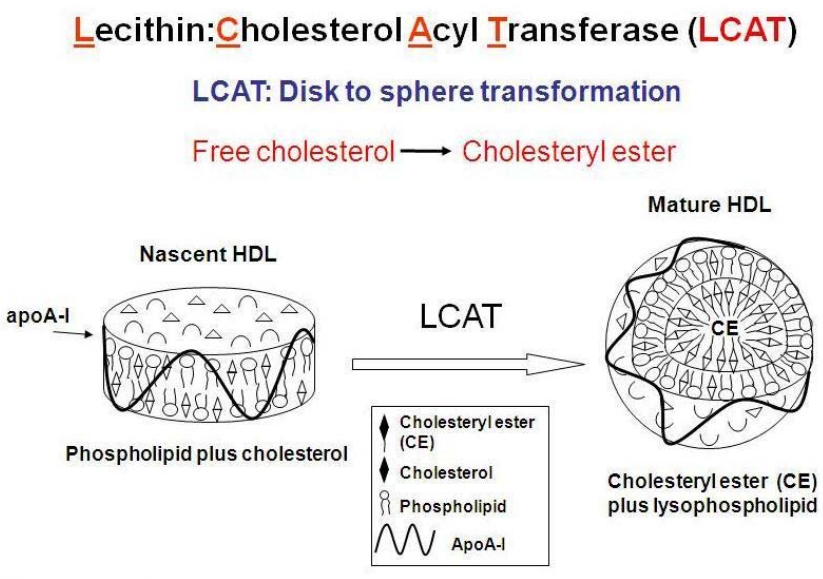

Fig 7: demonstrates Lecithin, Cholesterol Acyl Transferase (LCAT)

Familial HDL Abnormalities

As familial HDL-c deficiency is often associated withfamily histories of premature CAD, much effort hasbeen directed to understanding the molecular defect(s) involved there with [9A, 9B, 9C]. Increased HDL-c concentrations are generally accepted to be protective against the development of atherosclerosis and CAD, but studies have suggested that the underlying *cause* of the increased HDL-c may be important in whether it is protective. The familial hypoalpha-lipoproteinemiasare rare lipoprotein disorders characterized by low levels of plasma HDL[Fig:8]. However, despite of markedly reduced HDL levels, several of these

conditions, including Tangier disease, fish eye disease, and LCAT deficiency, are *not* associated with premature atherosclerosis. Moreover, some mutations in LCAT are known that resultsin increased CAD [10A, 10B].

Mutations leading to reduced CETP activity result in less CE being directed into Apo-B-containing particles (VLDL and LDL) and more remaining in HDL, resulting in increased HDL-c concentrations. Mutations leading to reduced hepatic lipase (HL) activity are rare and are associated with increased HDL-c concentrations and CAD.

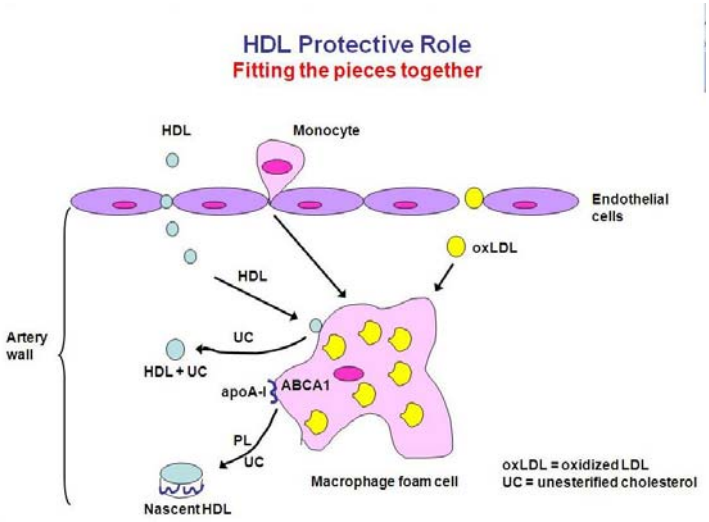

Fig 8: demonstrates HDL Protective Role in Human body

The ATP-binding cassette transporter A1 (ABCA1) protein regulates the efflux of cholesterol and phospholipids from the cell to apolipoprotein acceptors, the rate-limiting step in the removal of cellular cholesterol. Tangier disease is characterized by mutations in the ABCA1 gene, resulting in a defective ABCA1 protein and accumulation of cellular cholesterol, reduced plasma HDL-c, and increased risk for CAD; over 100 ABCA1 coding variants are known [11A, 11B, 11C, 11D]. The plasma in case of Tangier disease (TD) patients has essentially no ApoA-I-containing lipoprotein (LpA-I), which in normolipidemic plasma is the majority of HDL. Residual amounts of ApoA-I in TD plasma have electrophoretic pre1-LpA-I mobility.

CETP deficiency causes hyper-alpha-lipoproteinemia, that is, marked *elevation* of plasma HDL-c [12].While the extent to which CETP deficiency is actually associated with protection against CAD is unclear, it gave rise to the idea of inhibiting CETP as a therapeutic strategy[13A, 13B].

Primary (familial) Lecithin

Cholesterol acyltransferase (LCAT) deficiency is a genetic disease associated with corneal opacity, anemia, and proteinuria with renal failure. It is caused by the complete or near absence of LCAT activity.

ApoA-I is similarly characterized by a cysteine-for-arginine substitution, at position 151(R151C). These cysteine-for-arginine substitutions allow disulfide-linked dimers to form. The mutations appear to make the ApoA-I and ApoA-I proteins functionally more effective than normal ApoA-I. In several studies it has been found that, HDL formulations of recombinant ApoA-I-phospholipid complexes brought about rapid regression of a focal carotid atheroma and protection from myocardial infarction [14A, 14B].

HDL Infusion

Several infusion studies with nascent HDL particles (ApoA-I/phospholipid complexes) have demonstrated the prevention and regression of atherosclerosis [14A, 14B]. Extensive studies shown that, aortic atherosclerosis was established over 17 weeks in rabbits by balloon denudation and cholesterol feeding. Animals then received oral atorvastatin (5 mg/kg for 5 days) or two infusions of HDL particles (8 mg/kg ApoA-I) 2 days apart. Lesion size and composition were then assessed. HDL, but not atorvastatin, reduced lesion size by 36% [14B]. In patients with heterozygous familial hypercholesterolemia, a single infusion with recombinant pro ApoA-I particles (precursor of ApoA-I) resulted in a 34% sustained 10-day increase in cholesterol excretion, with a net removal of 5%–7% of total body cholesterol. Fecal sterol excretion was measured for 9 days before and 9 days after an intravenous infusion of the pro-ApoA-I liposome complexes. Plasma ApoA-I and HDL-c levels increased transiently during the first 24 h. Fecal excretion of cholesterol (neutral sterols and bile acids) increased in all subjects. Control infusions with only liposomes in two of the patients did not affect cholesterol excretion [15].

Another line of research is the use of peptides that mimic ApoA-I. ApoA-I is a large protein, comprising 243 amino acids, making its recombinant preparation difficult and expensive. Additionally, intravenous administration is necessary, which is inconvenient. Efforts have been made at finding peptide mimetics that produce similar results to ApoA-I, but that would be easier to manufacture and administer [16].

Life style modification

Much research suggests that the first step in increasing HDL-c levels should be life style modification. Regular aerobic exercise, loss of excess weight (fat), cessation of cigarette smoking,and changes in diet can all increase HDL-c levels(Ashen and Blumenthal, 2005; Kodama *et al*. 2007; Mooradian *et al*. 2006; Dullens *et al*. 2007). Dietary soy protein, soluble fiber, and plant sterol/ ester-containing

margarines have all been shown to favorably reduces the LDL: HDL ratio (Hermansen *et al*. 2003). Diets rich in whole grain foods tend to increase serum HDL-c levels, while decreasing serum LDL-c, triacylglycerol levels, and blood pressure (Anderson, 2003). The effects of soy isoflavones are somewhat controversial (Dullens *et al*. 2007). Polyphenols have become a focus of research for their role in the prevention of cardiovascular disease and ability to raise HDL-c. Polyphenols are common components of the human diet, present in many foods and beverages of plant origin, including tea, wine, cocoa, and soy. Epidemiological studies have repeatedly shown an inverse association between the risk of myocardial infarction and the consumption of tea or wine and intake levels of some particular flavonoids, but no clear association has been found in clinical studies with primary clinical endpoints (Scalbert *et al*. 2005; Manach *et al*. 2005). In fact, in twelve intervention studies with differing polyphenol sources, six showed no effect on lipid parameters and six showed an improvement (Manach *et al*.2005). Such inconclusive data has clouded the use of polyphenols (Zern and Fernandez, 2005). Moderate consumption of red wine (one or two drinks per day) has consistently been associated with a reduced risk of cardiovascular disease, a phenomenon to explain the so-called "French Paradox," the relatively low rate of vascular disease in the French population, despite a high level of saturated fats in their diet (Poussier*et al*. 2005; Zern and Fernandez, 2005; Renaud and de Lorgeil, 1992; Burr, 1995; Schäfer*et al*. 2007). The polyphenol resveratrol (trans-3,5,4' trihydroxystilbene), a stilbenoid antioxidant found in the skin of red grapes, wine, peanuts, and some berries, has been shown to exhibit cardio-protective properties (Wang *et al*. 2005). Thus, mild-to-moderate alcohol consumption appears to be reasonable for many people; in contrast hepatic dysfunction and addiction may outweigh the benefits. Improvement in HDL-c with life style changes may often be associated; however, the interaction between genes and the environment may influence the magnitude of any improvement. Thus, when life style modifications are insufficient, medications are used. Approaches to raise anti-atherogenic HDL-c have attracted much attention, because of expanding disease populations with low levels of HDL-c or high cholesterol, such as patients with type 2 diabetes, metabolic syndrome, dyslipidemia, and menopause.

To date, several medications that have been approved that increase HDL-c and new approaches are being sought.

Niacin is the most effective drug currently available to raise HDL-c levels. At higher pharmacological doses, niacin can reduce LDL-c, triglycerides [Fig:9, Fig:10], and apo-B, while increasing HDL-c and ApoA-I Chapman, 2005). These beneficial lipoprotein changes have been shown to translate for benefits, decreasing morbidity and mortality from cardiovascular causes (McCormack and Keating, 2005). Nicotinic acid, as vitamin B3, is available without prescription; however, side effects tend to be frequent when taken under suboptimal conditions. Extended- or prolonged-release niacin (Niaspan), marketed by Kos Pharmaceuticals, decreases flushing, niacin's most common side effect and increased HDL-c by ~25% from baseline at 200 mg/kg in clinical studies (Pal and Pillarisetti, 2007; McCormack and Keating, 2005; Birjmohun *et al*. 2004). With the discovery of the niacin receptor (HM74a, PUMA-G), several drug companies are working on developing novel agonists (Pal and Pillarisetti, 2007).

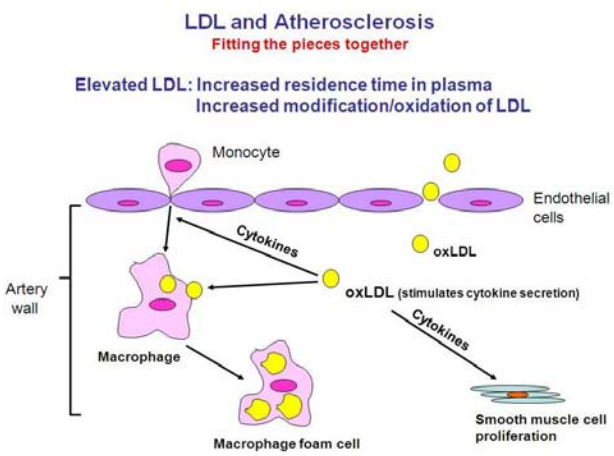

Fig 9: demonstrates the state in elevated LDL related with consequent effects

Therapetic Approaches

Hormone replacement therapy

Menopause is a pro-atherogenic state, associated with aincrease in the incidence of coronary artery disease (Schnatz and Schnatz, 2006). Estrogen replacement therapies, such as conjugated equine estrogen (CEE, Premarin), reduce the risk of CAD in postmenopausal women (Lamon-Fava *et al*. 2006). Hormone replacement therapy (HRT) is associated with increased ApoA-I and HDL and decreased LDL and total cholesterol levels. ApoA-I levels were increased most by use of estrogen alone (Lamon-Fava *et al*. 2006).

Rimonabant strategy

Rimonabant, a cannabinoid-1 receptor blocker, is being investigated for use in reducing body weight and improving cardiometabolic risk factors in overweight or obese patients (Forrester and Shah, 2006). In one randomized, controlled trial, the mean weight loss was 19 pounds at 2 years. In the high-dose group, 39% lost 10% of their initial body weight, compared with 15% in the low-dose cohort and 12% of those receiving a placebo. The number of patients with metabolic syndrome at baseline was reduced by about 50% with rimonabant 20 mg. Concomitant with the weight loss, the patients exhibited an 11% decrease in triglyceride and a

27% increase in HDL Cholesterol (Forrester and Shah, 2006). This drug is currently approved in many markets under the brand name Acomplia. However, in June 2007, the U.S. FDA's Endocrine and Metabolic Drugs Advisory Committee did not recommend approval of this strategyfor weight management.

CETP inhibitors

Cholesterol ester transfer protein (CETP) is a glycoprotein that facilitates the transfer of cholesteryl esters from HDL-c to Apo B-containing lipoproteins in exchange for triglycerides (Pal and Pillarisetti, 2007). Subjects with CETP deficiencies, because of CETP gene defects, have elevated plasma levels of HDL-c and ApoA-I. However theanti-atherogenic role of CETP is complex because, despite raising HDL-c levels, it also slows the metabolism of HDL-c (Rader, 2006, 2007a). To date, two CETP inhibitors, JTT-705 and torcetrapib, have been evaluated clinically and have shown efficacy of increase HDL-c (Rader, 2006, 2007a; Barter *et al*. 2007). In early clinical studies, torcetrapib showed a pronounced effect on plasma lipoproteins in patients with low HDL-c levels, and reduced the levels of LDL-c and apolipoprotein B, both as a monotherapy and in combination with atorvastatin (Rader, 2006, 2007a). After the phase II dose-ranging trials, torcetrapib, despite being associated witha substantial increase in HDL-c and decrease in LDL cholesterol, was also associated with an increase in blood pressure, and no decrease in the progression of coronary atherosclerosis (Nissen *et al*. 2007b). The lack of sufficiency may be related to the mechanism of action of this drug class or to molecule-specific adverse effects (Rader, 2007b; Barter *et al*. 2007). After demonstrating in phase II, no additional data has yet been published on JTT-705.

Inflammation has a fundamental role in mediating all stages of atherosclerotic disease. AGI-1067 (probucol monosuccinate, succinobucol) is being assessed for the treatment of restenosis and possibly atherosclerosis. The pharmacological activities of AGI-1067 are the ability to block the expression of oxidation-sensitive inflammatory genes, including genes that encode vascular cell adhesion molecule-1 and monocyte chemotactic protein-1.

Phospholipids

Phosphatidyl-inositol can stimulate reverse cholesterol transport by enhancing the flux of cholesterol into HDL and by promoting the transport of HDL-c to the liver and bile. Currently, phosphatidyl-inositol (PI) is being evaluated in human subjects. At doses as high as 5.6 g/day, PI demonstrated raise of HDL-c of 18% over a 2-week period, and a fall in triglycerides by 36% in fed subjects. This product is in clinical development (Burgess *et al*. 2005). CSL-111 is a reconstituted HDL, consisting of ApoA-I from human plasma combined with soybean phosphatidyl-choline, that resembles native HDL (Tardiff *et al*. 2007b). In a 183-patient phase II clinical trial, there was no significant reduction in atheroma or plaque volume, compared with the placebo, but there was a statistically significant improvement in the plaque characterization index and coronary score on quantitative coronary angiography [17].

Conclusions

The lipid hypothesis, now more than 100 years old, is based on the idea that dyslipidemia is central to atherosclerosis. Its validity was ultimately understood by major epidemiological studies, demonstrating that cholesterol levels were linearly related to coronary heart disease mortality. Further epidemiological studies showed an inverse relationship between blood levels of HDL-c and the incidence of clinically significant atherosclerosis; it appears that each 1 mg/dL increment in serum HDL-c is associated with a 2%–3% decrement in cardiovascular risk (Boden, 2000). While our understanding of the mechanism(s) by which HDL alters atherosclerotic disease remain(s) incomplete, it is believed that elevated levels of HDL increase the transport of cholesterol from arteries and tissues to the liver for excretion. Based on the RCT model (Fig. 1), ApoA-I is an attractive target for therapeutic intervention. Experimental manipulations to increase ApoA-I have been shown to reduce atherogenicity. Human ApoA-I is protective in transgenic animal models (Shah *et al*. 1998; Rubin *et al*. 1991) and infusion of ApoA-I prevents atherosclerotic lesions and leads to regression of atherosclerotic plaques in human patients. There is an ongoing need for novel therapies to increase the biosynthesis of HDL, to inhibit the progression of and even bring about regression of atherosclerosis. The development of a small molecule drug that increased endogenous ApoA-I would be a major advance in treating lipid-related cardiovascular disease. Targeting the patient's liver and small intestine to increase the transcription, synthesis, and secretion of ApoA-I is generally considered a promising approach for raising HDL-c levels. Currently, our ability to raise HDL is limited; life style, including dietary, changes, niacin, fibrates, estrogen, and to some degree, the statins do raise HDL, but not very potently. Several new drug classes are under investigation in this very active field.

Authors's contribution

Author has extended in depth research and exclusive study regarding the present spectrum that has been manifested to write him this review in favour of mankind and well-being of health science and cultivation.

In this paper, the author achieved extreme guidance favoring the in depth cultivation with a positive output from Partha Majumder, Biomedical Scientist and Systems Biologist, Former Principal Scientist (Helixinfosystems) and Former Head & Coordinator, Department of Applied Biotechnology and Bioinformatics, Sikkim Manipal University(CC:1637), Kolkata, India.

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