REVIEW OF LITERATURE

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Coronary Artery Disease in Young Indians

At the threshold of the new millennium coronary artery disease (CAD) is looming large as the new epidemic afflicting Indians at a relatively younger age with severe and diffuse form of lesions. Recently, the subject of CAD in Indians (referred as immigrants or Asian Indians or South Asians when outside India) has become a challenge for many research centers worldwide.[3,4] The prevalence of CAD has progressively increased in India during the latter half of the last century, particularly among the urban population.[5]The conventional risk factors namely hypertension, diabetes mellitus (DM), hypertriglyceridaemia, low levels of HDL-C, central obesity, lipoprotein-a (Lp a), high LDL-C, low levels of antioxidants (vitamin A, E, beta - carotene), rising affluence, rapid modernization associated with sedentary but stressful life style in summation are suggested as additional risk factors for CAD. They too do not fill all the blanks in information. Infections like Chlamydia in association with yet unknown agents may be the other etiological factors.

CAD in Indians the emerging scenario

The risk of CAD in Indians is 3-4 times higher than White Americans, 6-times higher than Chinese, and 20-times higher than Japanese.[6] Indians are prone as a community to CAD at a much younger age.[7,8] The disease pattern is severe and diffuse. Premature CAD is defined as cardiac events occurring before the age of 55 in men and 65 in women. In its severe form it is defined as CAD occurring below the age of 40 years. CAD is affecting Indians 5-10 years earlier than other communities. Indians also show higher incidence of hospitalization, morbidity, and mortality than other ethnic groups.[9]This global phenomenon of prematurity and severity suggests that the disease starts at an early age and has a malignant and progressive course.[10] (There is a parallel corollary between CAD in Indians and the malignant course of rheumatic fever, rheumatic heart disease with associated severe pulmonary hypertension observed by Indian cardiologists in the sixties). In the Western population, incidence of CAD in the young is up to 5% as compared to 12-16% in Indians.[11,12] In some studies from India,

the percentage of patients below the age of 45 years suffering from acute myocardial infarction (AMI) is reported as high as 25-40%.[13,14] In Great Britain the first AMI among Indians at age less than 40 years is reported 10 times higher than local Whites.[15] In Singapore, mortality from CAD below 30 years of age is 10 times higher in Indian than Chinese population of the same age group.[16] Angiographically, Indians have 15 times higher rate of CAD than Chinese and 10 times higher rate than local Malays below the age of 40 years.

Young patients from other communities do not show extensive disease,[17] whereas in young Indians there is often three vessel diseases with poor prognosis.[18] The post-infarction course is also worse in Indians as compared to whites. This is reflected by three-time higher rate of re-infarction and two-times higher rate of mortality.[19-21]

In an observation in the Middle East, out of patients admitted in CCU with acute MI below the age of 40-years, 80% were Indian expatriates as compared to 20% of native Arabs, whereas demographically Indian expatriates are about 10% of the local population.[22]

The prevalence of CAD is two-times higher (10%) in urban than in rural India.[23, 24] South Indians have higher prevalence, 7% in rural and 14% in urban areas. The vulnerability of urban Indians to CAD is possibly related to different nutritional, environmental, and life-style factors. The body mass index in urban Indians as compared to rural Indians is 24 Vs 20 in males and 25 Vs 20 in females. Unfortunately, the on-going urbanization of rural India is likely to narrow down these differences.

Migration from rural to urban environment and migration from India to industrialized countries is another special risk-factor for our people. Migration is usually associated with stress of seeking and maintaining the new job, stress of coping with the new job-expectations, and stress of competing with the peer group who is in the organization longer. New affluence is associated with sedentary life-style and higher consumption of

calories, saturated fats, salt, tobacco, and alcohol. These factors contribute to obesity, dyslipidaemias, hypertension, hyperuricaemia, and diabetes mellitus.

Therefore, there has to be high index of suspicion for CAD in Indians above the age of thirty years. The risk-factor evaluation must start earlier. Investigations like treadmill, stress echo, stress thallium, and coronary angiography should be more liberally recommended.

Risk factors (conventional and new)

There is a need for identifying and correcting the conventional risk factors like hypertension, diabetes mellitus, smoking, hyperlipidaemia, tobacco consumption, and central obesity at much younger age. Male sex is more prone to CAD but post menopausal females need special attention as they constitute a distinct sub-group at a high risk for CAD.

Hypertension remains a standard risk factor associated with CAD. Prevalence of hypertension is increasing in urban population, as compared to rural population. In metropolitan cities the prevalence is as high as 11%-27%. The prevalence of DM is about 20% in middle age and additional 20% may be having impaired glucose tolerance, even moderate elevation of glucose in Indians is associated with increased risk of CAD.[26] In contrast to decreasing mean cholesterol levels in the USA, the mean serum cholesterol level in urban Indians in rising. In Delhi, the mean serum cholesterol level has risen from 160 mg/dl in 1982 to 199 mg/dl in 1994. Indians even with lower levels of serum cholesterol have higher risk of CAD.

Smoking increases the risk of CAD by 3-5 times. In the first world countries, smoking has significantly decreased and is socially looked down-upon. In contrast, in India smoking is increasing particularly in the younger generation. As the demand is falling in the West, tobacco traders are dumping this atherogenic material in the Indian market. In the seventies, tobacco consumption in India per adult was 0.7 kg/year; it is likely to

increase to 0.9 kg/adult/ year. In India the consumption of tobacco is 6.1% of the world's total un-manufactured tobacco, 20% is in the form of *cigarettes*, 40% is in the form of *biddies* and the rest as smokeless tobacco products. Studies have shown that 40-50% of the males in India are smokers. For Indians, tobacco remains a major risk factor as it is used in different forms.

Central obesity, depicted by waist to hip ratio is an independent risk factor for CAD, even modest increase in body fat with central distribution increases the risk further.[26]

New risk factors

Lipoprotein-a (Lp-a) is now recognized as an independent risk factor for CAD. It is a genetic risk factor. It is not affected by any level of lifestyle modifications like changes in diet and exercise. Lp-a is ten-times more atherogenic than LDL-C. It promotes early atherosclerosis and thrombosis. Lp-a is a stronger risk-factor than DM for CAD in younger women. In Indians, both in India and abroad, the levels of Lp-a are higher as compared to the whites in Great Britain, suggesting a genetic propensity.[28] Lp-a levels in cord blood are higher among Indian newborns than Chinese newborns and this difference is also associated with a four-fold higher CAD – related mortality in Indians than Chinese in Singapore[29]. Lp-a level above 30 mg/dl are associated with three-fold higher risk of CAD. Lp-a levels over 40 mg/dl increases the risk associated with cigarette smoking by 1.9 times, with DM by 3.4 times, with high total cholesterol by 4.2 times, with hypertension by 4.6 times, with high TC/HDL ratio by 6.9 times, and with high homocysteinaemia by 9.3 times.[30]

In Indian patients with CAD, high triglyceride levels are found more often than high cholesterol levels. Triglycerides bring change in LDL particle size, density, distribution, and composition producing smaller, denser, and more atherogenic particles.[31] Estimation of triglyceride level gives an indirect measurement of LDL particle size. An increase of triglycerides from 90 mg/dl to 180 mg/dl is associated with doubling the incidence of CAD. Increase in triglycerides by 90 mg/dl has the same effect on coronary atherosclerosis, as increase in age by 10 years.[33] Earlier; there has

been an under-emphasis on the significance of triglycerides as a risk factor for CAD. Indians worldwide demonstrate a triad of high triglycerides with high LDL-C levels and low HDL levels. This triad combined with high levels of lipoprotein-(a) constitutes the deadly lipid quartet.

Higher levels of apolipoprotein-B (Apo-B) are reported in one third of Indians males. This factor in combination with low levels of HDL and hypertriglyceridaemia results in formation of small dense LDL which increases the risk of CAD more than three times.

The LDL-cholesterol types are described as phenotypes A, B, or C, which are genetically determined. Patients with LDL phenotype-B have predominantly small and dense LDL-particles which as mentioned above, constitute an important risk factor for CAD. A 75% prevalence of phenotype-B is seen in Asian Indians in contrast to 25% in White population. High levels of plasminogen activator inhibitor-1 (PAI-I) in Indians are reported in association with hypertriglyceridaemia and hyperinsulinaemia. This combination promotes thrombosis by impairing fibrinolysis.[34]

Insulin resistance syndrome (IRS) is an important risk factor for early development of CAD in Indians.[35] Indians, as compared to Europeans, have higher resistance to insulin mediated glucose uptake in association with hyperglycemia, hyperinsulinaemia, hypertriglyceridaemia, and low levels of HDL-C.

Serum fibrinogen is an independent and newer risk factor for CAD. Fibrinogen increases the blood viscosity and plays a key-role in thrombosis. Both factors promote coronary atherosclerosis.

Hyper-homocysteinaemia: Homocysteine is a sulfur containing amino acid which is a new and independent risk factor for CAD and stroke. Homocysteine causes vascular damage by its deleterious effects on endothelial functions and its pro-thrombotic, pro-oxidant, and mitogenic effects. The risks are comparable with the cigarette smoking and dyslipidaemias.

Infections and CAD: Various infections, viral and bacterial, have been implicated. Amongst them, *Chlamydia pneumoniae* is considered as an important risk factor for CAD.[37] This is so surmised because high antibody titers to Chlamydia lipopolysaccharide are found in patients of AMI. It is thought that AMI may be precipitated by exacerbation of *Chlamydia pneumoniae* infection. Atherosclerosis represents an exaggerated inflammatory reaction to injury of the endothelial layer of the arterial wall. A systemic infective episode produces generalized arteritis including coronary arteritis with diffuse lesions. These lesions may be further worsened by pro-atherosclerotic factors like smoking, hypertension, diabetes, and dyslipidaemias. The mechanism could be occurring other way round, i.e., coronary endothelium which has already developed atherosclerotic plaques due to conventional risk factors, on getting further inflamed by a systemic infection, undergoes aggravation of plaque activity and thrombosis, precipitating an acute coronary event. Whether fuel is poured over the fire or fire is added to the fuel is a subject for further research.

LIPOPROTEIN (a)

LIPOPROTEIN (a) was discovered in 1963 by Kave Berg while experimenting with rabbits immunized with human LDL.[40] The association of Lipoprotein (a) with CAD was initially demonstrated in 1974. It constitutes an important inherited risk factor for atherosclerosis [40,41] and is also regarded as biological marker for familial CAD.[42,43]

STRUCTURES OF LIPOPROTEIN (a) :- Lipoprotein (a) [Lp (a)], is present only in humans, Old World nonhuman primates, and the European hedgehog. Lp (a) has many properties in common with low-density lipoprotein (LDL) but contains a unique protein, apo (a), which is structurally different from other apolipoproteins. The size of the apo (a) gene is highly variable, resulting in the protein molecular weight ranging from 300 to 800 kDa; this large variation may be caused by neutral evolution in the absence of any selection advantage. Apo (a) influences to major extent metabolic and physicochemical properties of Lp (a), and the size polymorphism of the apo (a) gene contributes to the pronounced heterogeneity of Lp (a). There is an inverse relationship between apo (a) size and Lp (a) levels; however, this pattern is complex. For a given

apo (a) size, there is a considerable variation in Lp (a) levels across individuals, underscoring the importance to assess allele-specific Lp (a) levels. Further, Lp (a) levels differ between populations, and blacks have generally higher levels than Asians and whites, adjusting for apo (a) sizes. In addition to the apo (a) size polymorphism, an upstream pent nucleotide repeat (TTTTAn) affects Lp (a) levels.[44]

It is modified form of LDL molecule with apo B-100 covalently linked and bound to a molecule of apoLp (a) i.e. Apo (a) by a single disulphide bridge to form Lp (a). The apo (a) chain contains five cystine rich domains known as kringles. The forth kringles is homologous with the fibrin binding domain of plasminogen, a plasma protein that dissolves blood clots when activated. It is identical to LDL except for the addition of apo (a). The physiological function of Lipo (a) is not known.

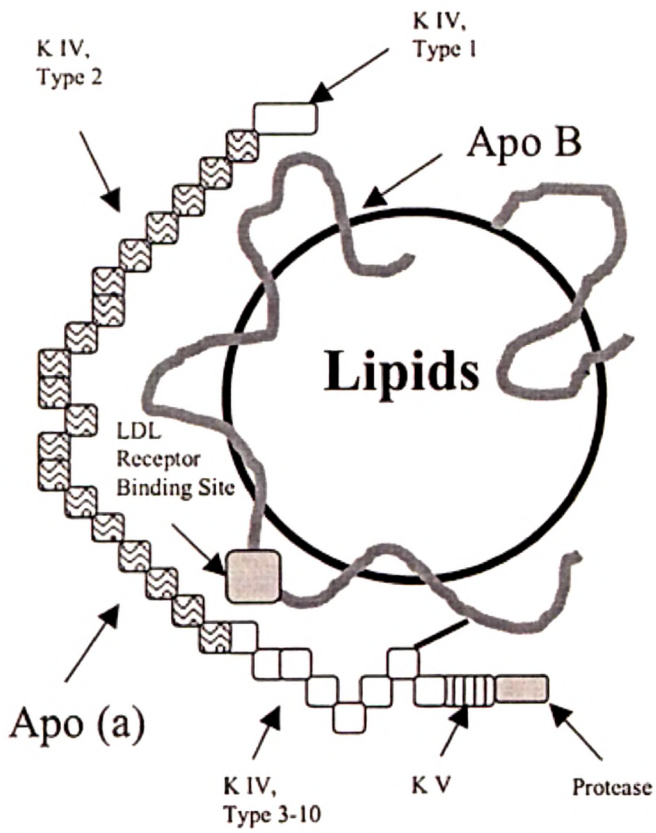

Figure 1. Model of Lp (a). The LDL-like moiety consists of a lipid core of cholesterol esters and triglycerides surrounded by a surface layer of phospholipids and free cholesterol. In addition to lipids, it also contains one molecule of apolipoprotein B, which is linked to apolipoprotein (a) through a single disulfide bond. The putative LDL receptor binding domain of apo B is shown. The apo (a) moiety consists of a single copy of kringles KIV, types 1 and 3 to 10, kringle V, and a protease domain analogous to plasminogen. In addition, it contains multiple copies of kringle IV, type 2.

Lipoprotein (a) [Lp (a)] was first described 40 years ago, and interest in this entity is largely derived from its putative role as a cardiovascular risk factor.[45-47] Underlying this concept is the realization that Lp (a) has many properties in common with low-density lipoprotein (LDL), a well-established atherogenic factor for coronary artery disease.[48,49] Thus, the composition of the lipid moiety of Lp (a), including its cholesteryl ester-rich core, is similar to that of LDL, and the density distribution of the lipid moiety of Lp (a) in a given subject closely mirrors that of LDL.[50] Furthermore, like LDL, each particle of Lp (a) has 1 molecule of apolipoprotein B-100 (apo B-100); both apolipoprotein B (apoB) and the lipid core are pro-atherogenic.[51] Also, Lp (a) clearance rates are similar to those for LDL.[52,53] However, Lp (a) contains a unique protein, apolipoprotein (a) [apo (a)], which is structurally different from other apolipoproteins, having a hydrophilic, carbohydrate-rich structure with no amphipathic helices.[54,55] Apo (a) is linked to apoB through a single disulfide bond connecting their C-terminal regions (Figure 1).[56-59]

The presence of apo (a) influences to a major extent metabolic and physicochemical properties of Lp (a).[60-62] Notably, the cysteine residue in apoB involved in the covalent bond between apoB and apo (a) is close to the postulated LDL receptor-binding region of apoB.[63,64] It appears from many clinical studies that Lp (a) levels are not affected by LDL receptor activity,[65,66] suggesting that the large, carbohydrate-rich apo (a) protein introduces a charge and/or stearic interaction affecting the binding potential of apoB in Lp (a) for the LDL receptor. This could at least partly explain why Lp (a) plasma levels are mainly determined by the synthetic rate in contrast to LDL in which catabolism through the LDL receptor is an important regulator of plasma levels, although overall clearance rates are similar for the 2 lipoprotein fractions. Lp (a) levels are particularly affected by apo (a) synthetic rate, which is subject to strong genetic regulation. Because of this strong genetic impact, Lp (a) plasma levels are affected only to a minor extent by age, sex, and environmental factors.3

Lp (a): MOLECULAR PROPERTIES: - Lp (a) is very heterogeneous and the underlying reasons for this heterogeneity were uncovered by the elegant work on the gene structure of apo (a) by Lawn, Scanu, and their collaborators.[68] They reported an analogy between the apo (a) and plasminogen genes; both genes have coding sequences for loop structures stabilized by intrachain disulfide bonds, so interestingly, the sequence coding for one of these K called kringle (K) domains. The plasminogen gene contains coding sequences for 5 different K domains (K1 to K5), and 2 of these are present in the apo (a) gene, K4 and domains, K4, is repeated many-fold in the apo (a) gene.[68-70] Altogether, the apo (a) gene has 10 different types of plasminogen- like K4 domains, referred to as K4 type 1 through 10. K4 types 1 and 3 to 10 are present as single copies, whereas K4 type 2 is present as multiple copies, varying in number from 3 to 40 copies. Each kringle contains 80 to 85 amino acids and has a molecular weight of -10 kDa, and the K4 repeat unit is thus unusually large. This heterogeneity in apo (a) gene size corresponds to a size variation in the apo (a) protein and apo (a) size isoforms containing from 12 to _50 K4 motifs have been reported, corresponding to a protein molecular weight ranging from 300 to 800 kDa. The size variability of apo (a) impacts on Lp (a) levels; there is a general inverse relation between apo (a) size and Lp (a) levels.[71,72] Thus, smaller apo (a) sizes tend to correspond to higher plasma Lp (a) levels; however, this pattern is complex. For a given apo (a) size, there is a considerable variation in Lp (a) levels across individuals. Lp (a) is found only in humans, in Old World nonhuman primates, and in the European hedgehog. The hedgehog version of apo (a) appears to have evolved separately from the primate and human apo (a) versions, because it contains the plasminogen K3 domain instead of the K4 domain and is not subject to size heterogeneity. Thus, although apo (a) is novel from an evolutionary standpoint, it appears nevertheless to have emerged twice. Despite this, there is currently a profound lack of understanding of any physiological function for Lp (a).

GENETIC DETERMINANTS OF Lp (a):- Serum Lp (a) levels are largely genetically determined with a single apo (a) gene, localized to the long arm of chromosome 6, accounting for more than 90% of variations in its serum level. Only part of plasma levels of Lp (a) is under genetic control while the other part is environmentally influenced by factors like renal function, hormonal status, age and dietary habits.

Lp (a) levels are also reduced by treatment with N-acetyl cystine, danazol and allylesterol;[73,74] Nicotinic acid and Neomycin also decrease levels of Lp (a), and are used for therapeutic purpose.[75] LDL aphaeresis is useful modality of treatment of patients of homozygous familial hypercholesterolemia and ordinary hypercholesterolemia.

Lp (a) concentrations are resistant to most forms of LDL-lowering therapy. An exception is the antihyperlipidemic drug, niacin, which decreases Lp (a) as well as LDL cholesterol. In addition anabolic steroids and alcohol decrease Lp (a). The fact that Lp (a) is not affected by most lipid lowering drugs suggests that the regulation is different from that of LDL. Although Lp (a) and LDL are rather similar in structure the 2 lipoproteins are metabolized differently. Lp (a) does not have a precursor lipoprotein, because it is secreted in the blood directly from the liver. Lp (a) formation is a 2-step process involving an initial noncovalent interaction between apo (a) and apoB 100 that precedes specific disulfide bond formation. A possible coupling between the metabolism of triacylglycerol-rich lipoproteins (TRL) and that of Lp (a) was suggested. An inverse relation between Lp (a) and plasma triacylglycerol (TAG) was reported in hyperlipidemics. Although an interaction between TRL and Lp (a) is plausible, the mechanism is not fully understood. Degradation of Lp (a) may be mediated through VLDL receptors or apo (a) may be cleaved from an Lp (a) particle in the kidney, leaving the lipid and apoB components to be cleared through the LDL receptor.

LABORATORY ESTIMATION AND PLASMA LEVEL:-

The major source of circulating plasma Lp (a) level is derived from liver.[76]

Laboratory estimation was obtained from radioimmunoassay, immunoelectrophoresis and by ELISA method. There is marked variation in serum levels fluctuating from <0.1 mg/dl to a maximum of >150 mg/dl.[77,78] In the Framingham offspring study, distribution of serum levels of Lp (a) in Caucasians was found to be highly skewed. 10% had serum values of <1 mg/dl and more than 50% had, 10 mg/dl.[79]

A number of factors affect the serum levels including renal failure, nephrotic syndrome and alcohol consumption. Moderate alcohol drinking lowers plasma Lp (a) levels;[76] Niacin and hormone replacement therapy lowers Lp (a) levels.

FACTORS AFFECTING Lp (a) CONCENTRATION:-

1. PHYSICAL FACTORS:
   Age: High risk factor in young age.
   Menopause:- Estrogen reduces Lp (a) level.
2. CHEMICAL COMPOUNDS AND DRUGS :-
   Estrogen:- Reduces Lp (a) level
   Niacin:- Reduces Lp (a) level.
   Neomycin:- Additive effect along with Niacin to reduce Lp (a) level.
3. DISEASE:
   Myocardial infarction:- Risk factor for MI in young age.

Lp (a) AND ATHEROSCLEROSIS:-

Lp (a) promotes atherosclerosis by following mechanisms:

1. The VLDL receptors found on the macrophages present in atherosclerotic lesions can bind to and mediate the catabolism of Lp (a) by endocytosis, leading to its degradation within lysozomes. This would lead to a cellular accumulation of lipids within macrophages. Supporting this hypothesis is the observation that Lp (a) is ubiquitous in human coronary Atheroma, co-localizes with plaque macrophages, and is detected in large amount in tissue

from culprit lesions in patients with unstable compared to stable coronary artery disease.

2. Binding to endothelium and components of the extra cellular matrix, leading to endothelial dysfunction due to selective impairment of vasodilators capacity of receptor mediated endothelial stimuli.
3. Enhancement of expression of intracellular adhesion molecule 1, resulting in the recruitment of monocytes to the vessel wall and binding to macrophages. This can promote foam cell formation and the localization of Lp (a) in atherosclerotic plaque.
4. Enhancing susceptibility of LDL cholesterol to oxidative modification.
5. Inhibition of thrombolysis, which may prevent activation of transforming growth factor B, an inhibitor of vascular smooth muscle proliferation.
6. Interference with fibrinolysis by competition with plasminogen for binding sites on molecules and cells.
7. Prothrombotic mechanisms: Given the extensive sequence homology between apo (a) and plasminogen, (euton et al 1987, Mc Lean et al 1987), it has been suggested that much of the atherogenic potential of Lp (a) derives from interference in normal pathways of thrombolysis, to predispose patients to acute thrombotic complications. Prothrombotic effect of Lp (a) include interference with its binding to endothelial cells monocytes & thrombospondin, interference with the binding of tissue plasminogen activator to fibrin; & stimulation of synthesis of PAI – 1 (reviewed by stein & resenson, 1997, chapmann et al 1994, Loscalso 1990.)
8. Other hypothesis includes a role for Lp (a) in cholesterol delivery to the injured vessel wall & stimulation of vascular cell proliferation. Pathogenic & laboratory evidence includes observations that Lp (a) binds lipoproteins containing apo B, avidly binds to arterial proteoglycans & fibronectin, accumulates in atherosclerosis lesions, stimulates SMC proliferation & promotes cholesterol accumulation in cells.
9. With oxidation on modification by malondialdehyde, Lp (a) becomes a ligand, both in vitro & in vivo, for the scavenger receptor, & macrophages form cells

may express a distinct Lp (a) clearance receptor. Lp (a) might interfere with the normal degradation of cholesterol by way of LDL receptor or itself be targeted to early atherosclerotic lesions, possibly through the macrophage scavenger receptor.

10. Oxidized Phospholipids: Relation to Lp (a) - Recently, a new possible mechanism for apo (a) atherogenicity has been suggested. In a series of studies, Witztum et al have demonstrated convincingly that key oxidized phospholipids are preferentially associated with Lp (a). Proinflammatory, oxidized phospholipids are covalently bound to kringle V in apo (a), a portion of apo (a) associated with macrophage IL-8 production. These results suggest that Lp (a) may act as a preferential acceptor that tightly binds oxidized phospholipids transferred from tissues or from other Lipoproteins. This could imply that Lp (a) functions as a scavenger absorbing potentially deleterious oxidized lipids, preventing an increased uptake in the vessel wall of other lipoproteins, primarily LDL, containing this factor. However, the presence of oxidized phospholipids in Lp (a), potentially being taken up by the vessel wall, could also accelerate development of atherosclerosis. Because kringle V is present as a single copy in the apo (a) molecule, the results suggest an apo (a) size-independent potential for binding of oxidized phospholipids, although it is possible that apo (a) size can affect the binding site through conformational changes. Notably, Lp (a) levels have been found to be higher among white centenarians, raising the possibility that Lp (a) may serve as a longevity factor, although opposite results have been reported in a Japanese cohort.
11. The interaction of Lp (a) with the vascular endothelial barriers has been serviced by Nordestgaard (1996). Lp (a) appears to enter the intima at about the same rate as LDL but may be retained there to a greatest extent, particular at the sites of injury.

Lp (a) and CAD:

Lp (a) is considered to be 10 times more atherogenic than LDL-C.[80] Relative risk of CAD is increased three fold in males if Lp (a) levels are above 30 mg/dl.[81,82] Adverse effects are enhanced by High LDL-C and low values of HDL-C. There is six fold increased when LDL-C also elevated. Men with LDL-C >317 mg/dl and Lp (a) > 30 mg/dl have a 16 fold increased odds ratio of having CAD verses those having an LDL-C levels of >130 mg/dl, and Lp (a) levels of < 10 mg/dl. The levels also correlate with presence and extent of severity and score of atherosclerotic lesions on coronary angiography.[83]

Lp (a) and Diabetes:

Diabetes is one of the most important disease, which has got significant impact on lipid profile. Studies from south India have shown good correlation between Lp (a) levels and risk of CAD in NIDDM.[84] Lipoprotein (a) is shown to be a powerful, independent risk factor for CAD in type 2 DM and this association is independent of all other known risk factor including TC, LDL-C, HDL-C and triglyceride.

Treatment:-

Primary goal of treatment: LDL reduction. If LDL concentration cannot be reduced to less than 130 mg/dl. Specific Lp (a) lowering therapy can be initiated in appropriate patient with Nicotinic acid (3-4 gm/day) or Neomycin (2-3 gm/day) in divided doses.

Nicotinic acid reduces Lp (a) level by 38% versus 24% by Neomycin combined therapy produces addictive effect lowering Lp (a) and LDL by 45%

Estrogen replacement therapy is the treatment of choice for postmenopausal women with Lp (a) levels excess who do not have contraindication to its use. ERT reduces Lp (a) levels up to 50%. Progesterone mitigates this effect. ERT appears to have more favorable effects on outcome in women with High Lp (a) levels then in women with low levels. Statins and bile sequestrating agents do not reduce Lp (a) levels. Most fibric acid derivatives do not lower Lp (a) levels, except for Bizafibrates.

LDL aphaeresis in patients with homozygous familial hypercholesterolemia and in ordinary familial hypercholesterolemia can cause profound lowering of LDL-C.

RISK FACTORS FOR CAD

Current prediction estimates that by 2020, cardiovascular disease, notably atherosclerosis will become the leading global cause of total disease. The systemic study of risk factors in humans began in mid century. The risk factors that emerged from such studies have seen classified into two categories. [85]

UNMODIFIABLE RISK FACTORS:

Age:

Gender: Male

Genetics

MODIFIABLE RISK FACTORS:

By life style:

- smoking
- obesity
- physical inactivity

By pharmacological and or life style:

- Lipid disorders
- HT
- Insulin resistance
- Estrogen status
- Mental stress

NOVEL RISK FACTORS:

- Homocysteine
- Fibrinogen
- Lp (a)
- Markers of fibrinolytic function: PA-1, t-PA
- Markers of inflammation: CRP, ICAM-1, IL-6

HYPERCHOLESTEROLEMIA:

This is considered as one of the prime risk factor for CAD. The earlier the age of detection, greater the risk of CAD. Elevated serum cholesterol is casually associated with risk of CAD specifically a 10% increase in serum cholesterol is associated with a 20-30% increase in risk of CAD.[85]

In man it has been found that 41% variants in CAD mortality was related to variation in serum cholesterol, 32% was related to variation in ratio of total cholesterol to HDL-cholesterol. It is difficult to define safe basal level of serum cholesterol. A low risk level from the point of view of primary prevention should ideally be LDL-C <130 mg/dl, HDL >40 mg/dl, TG <150 mg/dl.

SMOKING:

Smoking increases CAD mortality by 50%, it doubles the incidence of CAD and the risk increases with age, and number of cigarettes smoked. Similar risk has been observed among women.

Smoking is a leading preventable cause of death and CAD worldwide. Those who quit smoking decrease the risk by 50% in 1-2 years and to normal levels by 5-15 years. Smokers have lower HDL-C levels and high VLDL and triglyceride levels.

HYPERTENSION:

A well-established risk factor for CAD, both elevated SBP and DBP are associated with increased risk. A 7 mm Hg increase in diastolic blood pressure over any baseline reading was associated with 27% increased in CAD risk and 42% increase in stroke risk.[86] Similarly lowering diastolic BP by 5-6 mm Hg results in a 42% reduction in risk of stroke and 15% reduction in risk of CAD.

DIABETES:

It is a major risk factor for CAD. By age 40 years, CAD is the leading cause of death in both diabetic males and females. Age adjusted rates of CAD are 2-3 times higher in diabetic men and 3-7 times higher in diabetic women than their non-diabetic

counterparts. In Danish Stars Hospital study, mortality from myocardial infarction alone was 12.5% after 35 years of diabetes regardless of age of onset.[87]

HDL AND TRIGLYCERIDES:

HDL is an important independent predictor of CAD, every 1 mg decrease in HDL, causes 3-4% increase CAD. The ratio of HDL to LDL may be an even better predictor of CAD than LDL alone.

Fasting triglyceride levels represents a useful marker of the risk of CAD particularly when the HDL levels are also considered.

PHYSICAL INACTIVITY:

Regular physical activity protect against CAD. The risk of CAD in sedentary individuals was twice that in active individuals after controlling other coronary risk factors. The benefits are through weight reduction, BP and cholesterol reduction.

OBESITY:

Obesity appears to have an independent risk for CAD, even after controlling the other risk factor. A higher BMI is associated with an increase in all the risk factor of CAD and stroke. The distribution of body fat may also play role, with abdominal adiposity posing a substantially greater risk in both men and women. A waist circumference of 35 inches in women and 40 in men is an easily measured marker of CAD risk.[88]

ESTROGEN AND SEX:

A well-established fact that men have a higher risk of CAD than women. The latter have high HDL-C level and lower LDL-C level. However there is striking increase in CAD in females after menopause. The beneficial effects are attributed to the higher estrogen levels in females, which drops after menopause.

ALCOHOL:

Heavy alcohol intake increase total mortality. However moderate alcohol consumption has a protective effect in CAD, 1-2 drinks/day, increases HDL, improves fibrinolytic capacity and platelets aggregation.

DIET:

Low fat diet decreases risk of CAD. Saturated and Trans fatty acids appears to increase the risk of CAD.

PSYCHOLOGICAL FACTORS:

Type 'A' personality traits seem to predispose to CAD. Chronic emotional distress alters autonomic discharge and increase BP. Depression, absence of social support and anger appear to contribute to an elevated risk of CAD.

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS WITH CAD.

The intimate involvement of lipid at each step in the development of atheroma and its potentials for manifestations of disease has been brought out from extensive studies. Atheroma is circumscribed focal lesions in the intima of arteries.

The vascular endothelium is endowed with special properties of contact inhibition, tight junction and elaboration of autacoids like, nitric oxide (NO), adhesion molecules and thrombolytic factors. Several cytokines thus modulate the vascular tone and maintain the lumen for free flow of blood. Endothelial injury or dysfunction often alters these properties. Injury may occur from physical stress, infective agents, toxins or immunogenic inflammations.

Endothelial denudation leads to insudation of lipids and Atheroma formation. Endothelial dysfunction initiates the process. Hyperlipidaemia and excess of modified lipoprotein fractions have been recognized as important causes of endothelial dysfunction that leads to exaggerated transcytosis of lipoproteins mainly LDL more so, of the small dense type as well as chylomicron remnants, VLDL and Lp (a) from

plasma into the sub endothelial zone of arterial intima. They are bound to proteoglycans, which present their egress from this site.

Within the intima, inaccessible to circulating plasma antioxidants, LDL particles are acted upon by oxygen free radicals from the surrounding tissue and form oxidized LDL (OX LDL) from minimally modified LDL. Both oxidized and glycated LDL tend to stimulate the endothelial cells to release adhesion molecules (E-Selectin,VCAM, ICAM), leading to pallisading monocytes and T lymphocytes along the endothelial surface, chemo attractants elaborate similarly, induce migration of the leucocytes across the endothelium. Under the influence of OX LDL the monocytes turns into macrophages and develop scavenger, receptive for modified LDL molecules. Inhibition of lipids transforms such macrophages to foam cells.

FATTY STREAKS:

Accumulation of foam cells in the sub-endothelium appears as fatty dots or fatty streaks on the intimal surface of aorta in early life. Coronary arteries manifest fatty streaks by 3rd decade some may regress, but some will progress further to 'plaque' formation.

FIBROFATTY PLAQUE:

With time, the foam cells degenerate, releasing their contents into the extra cellular space within the intima, successive foam cell formation and release of contents leads to the creation of a lipid pool. Meanwhile, the released growth factors stimulate the proliferation of smooth muscle in the intima, as well as those recruited from media. These smooth muscle cells elaborate plenty of collagen, while inflammatory cytokines induces proliferation of fibroblast and lying down of fibers and intestinal matrix.

These changes increase the size of lesions and they stand out as plaque over intimal surface, such lesions are common at branch point. Typically these plaques contain 40% lipids by volume, the rest being collagen tissue matrix and smooth muscle cells. The lipids are separated from vascular lumen by fibrous cap.

ADVANCED PLAQUE:

Calcification is common in advanced plaques. The deposits may be scanty, patchy, scarring cap develops from excessive fibrosis, cracks, fissures and erosion may develop over the fibrous cap. Endothelial denudation leads to platelet aggregation on its surface, rupture of cap exposes the circulating coagulation factor to highly thrombogenic core of the plaque leading to vascular thrombosis. Exudation of the core into the lumen may cause obstruction to blood flow in medium sized muscular arteries whereas in larger vascular channels the material may flow out as cholesterol emboli. Hemorrhage into the plaques may occur from thin walled vascular channels within or blood may enter the plaque from the circulation through the dents in the fibrous cap.

Plaques with a tendency to develop complications leading to vascular occlusion are described as unstable. It has been observed that such plaque usually have large lipid cores and hence more susceptible to plaque rupture in contrast to those with excess calcification and scarring. Large lipid pools induce plaque instability and precipitate event such as unstable angina, and myocardial infarction and cerebral thrombosis.

Lp (a) and CAD

A number of studies carried out both in India and abroad, studying the level of Lp (a) and its relation to CAD.

The coronary artery disease in India study first reported the existence of high levels of Lp (a) in Asian Indians when they compared the Lp (a) levels of 141 Asian Indian physicians with 136 white physician in U.S. Lp (a) levels >30mg/dl were found in 25% Asian Indian and in 17% whites.[89]

Sandholzer et al reported Lp (a) levels twice as high in Asian Indians compared to Caucasians, Malaysians and Chinese residents of Singapore from 1150 subjects.[90]

Bhatnagar et al have reported nearly identical high mean level of Lp (a) among Asian Indians living in the UK and their siblings in India.[91]

Sanket et al have confirmed that mean Lp (a) level among Asian Indians is higher than whites with CAD and have also found a good correlation of levels of Lp (a) with the extent of CAD in Indian. It was found that Lp (a) levels were nearly double in 15-30 years old sons of Asian Indians suffering from CAD compared to similar aged sons of white parents -19 mg/dl versus 10 mg/dl suggesting an important role of Lp (a) in CAD.[92]

Bahl et al, from Delhi, reported that only plasma lipids do not predict the severity of atherosclerosis and large vessels disease as demonstrated in angiography and only a trend for higher Lp (a) values in patients with severe CAD.[93]

A study from new Delhi, also showed higher lipoprotein (a) levels in 114 consecutive patients undergoing coronary angiography with mean levels of 42 mg/dl.[94]

Singh et al from Delhi have reported that Lp (a) alone would correctly discriminate a CAD individuals for control subjects by 95%. They also found that in female's atherothrombotic potential of lipoprotein (a) remains suppressed before menopause but after this stage women lose their advantage.[95]

Mary sed et al found that in a prospective population based study, of asymptomatic middle aged men in UK that serum Lp (a) levels were an independent risk factor for coronary events.[96]

A study by Sigudsson G et al, of 1332 patients, who were followed for occurrence of coronary events showed that Lp (a) was an independent risk factor for the occurrence of myocardial infarction in men aged 45 to 72 years.[97]

The Quebec cardiovascular study found that high Lp (a) levels appeared to increase risk associated with other lipid risk factors.[98]

Studies by Boston et al have also shown that Lp (a) is a risk factor for CAD in younger men and also women.[99]

Michael Shilpak et al have found Lp (a) to be an independent risk factor for recurrent CAD in postmenopausal women and that treatment with estrogen and progesterone lowers Lp (a).[100]

Recently a comprehensive lipid tetrad index has been proposed by enas as the best estimate of the total burden of dyslipidaemias.[101] It is derived by the product of cholesterol, triglycerides and Lp (a) value divided by HDL level and may estimate the need for various cut off points and ratios involving these lipids. A high index indicates a highly atherogenic lipid profile and warrants aggressive treatment.

Lipid tetrad index of Asian Indians:-

Population	Index=$\frac{TC \times TG \times Lp(a)}{HDL\text{-}C}$	TC mg/dl	TG mg/dl	Lp (a) mg/dl	HDL mg/dl
Asian Indians					
Men in India	12899	189	182	18	48
Women in India	10814	196	151	19	52
Asian Indians					
Men in UK	20629	251	186	19	43
Women in UK	15615	239	147	20	45
Asian Indians					
CAD in UK	34720	236	197	33	41
White CAD in UK	18085	233	163	20	42

Lipoprotein (a) Is an Independent Risk Factor for Myocardial Infarction at a Young Age Martin Sandkamp,' Harald Funke, Helmut Schulte, Eckhard KOhler, and Gerd Assmann". We quantified Lipoprotein (a) [Lp (a)] immunochemically in Young (<46 y) male survivors of myocardial infarction and in Age-matched controls recruited from participants of the Prospective Cardiovascular study. We further determined apolipoprotein E polymorphism and measure triglycerides, total cholesterol, high- and low-density lipoprotein cholesterol (HDL and LDL), and apolipoproteins Al, All, and B in the serum of these subjects. Lp (a) concentrations in serum were not correlated with other well-recognized risk factors for early myocardial infarction such as apolipoproteins Al and B, LDL cholesterol, and HDL cholesterol. Apolipoprotein E polymorphism did not affect Lp (a) concentrations, but had a major influence on apolipoprotein B concentration. Lp (a) concentrations were not influenced by age. Our data suggest that (a) an increased concentration of Lp (a) constitutes an independent risk factor for early myocardial infarction and *(b)* the concentrations of Lp (a) and LDL cholesterol (apolipoprotein B) in serum are under separate metabolic control.[102]

Recent studies also shown the role of Lp (a) in CAD in Indian patients Geetanjali et al have found a level of 33.4±26.1 mg/dl in angiography proven coronary artery disease.[103]

A study by Reddy Vit. K et al, from Hyderabad of CAD patients showed a mean level of 26.4 mg/dl.[104]

A study of unstable angina patients from Amristsar by Dr. BAL B.S. Et Al showed mean level of 36.2±4.2 mg/dl.[105]

A recent study from Kolkata by Guha et al of 30 proven CAD patients, showed a very high lipid profile tetrad index of 52350.2 and a mean Lp (a) levels of 59.2 mg/dl.[106]