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Lipoprotein (A) the Rebellious: Novel Perception of the Biological and Clinical Importance

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Abstract:

In the 1960s Norwegian physician the Kare Berg was revealed lipoprotein (a) in the lab. Meanwhile, we have significantly developed ourfact of cardiovascular disease of and lipid. Lipoprotein (a) is a mysterious variant of low density lipoprotein with an extra-large glycoprotein as apoliporoteinapo (a) tangled to it in structurethatuttered by hepatocytes and assemblage of apo (a) and low density lipoprotein take place on external surface of liver cell. Plasma concentration of lipoprotein (a) ranges from < 1 mg to > 1,000 mg/dL which can be resolute by using of monoclonal antibody-based procedures. Lipoprotein (a) levels more than 20-30 mg/dL are associated with a two times threat of emerging coronary artery disease. Generally, the greater lipoprotein (a) levels of African subjects are more likely to yield the coronary artery diseases than that of Caucasians and Orientals, are not concomitant to it. Age and sex have slight impact on lipoprotein (a) levels. Lipoprotein (a) homologous to plasminogen may be lead to intrusion of the fibrinolytic coagulation activity, accountable for an atherogenic mechanism of that lipoprotein. Though, accretion of lipoprotein (a) unswervinglyon intima of the arterial wall is also being furthersusceptible to oxidation than low density lipoprotein. Most prospective studies have confirmed lipoprotein (a) as a predisposing factor to atherosclerosis. Lipoprotein (a) only furthermost conjoint sovereign hereditarily genetic contributing risk elements for cardiovascular disease has been recognized by genome-wide association study and othersmeta-analytic studies. Raised lipoprotein (a)level is an important biomarker for atherosclerotic. For high lipoprotein (a) levels we contemporary to explain the metabolism, pathophysiology, existing and imminent medical interferences.

Keywords: Lipoprotein A, Novel, Diabetes, Stroke, Pathogenicity

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INTRODUCTION:

Initially Lipoprotein (a) was categorized as well asrecognized as a "low density lipoprotein variant". Apo (a) as the added protein of lipoprotein (a)familiar as a assumed risk factor for atherosclerosis diseases like coronary arterial disease and stroke.Just in primates lipoprotein (a) consider as an exceptionalclassof dispersal creature existent.Lipoprotein (a) is the chief plasma lipoprotein transporter of oxidized phospholipids which responsible for plasminogen inactivation, and stimulates smooth muscle cell proliferation and lead to inflammatory changes in most of the animals studies. Currently, the most important impact on lipoprotein (a) is that the apo (a) gene size is extremely polymorphic and is a foremost interpreter of lipoprotein (a) levels. Lipoprotein(a) levels ominously do not modify outdated lipoprotein-lowering drugs. However, at present in general population screening for raised lipoprotein (a) is not endorsed. At least it should be measured once in subjects to prevent the risk of cardiovascular disease. Currently, though, evidence from lipoprotein (a) lowering trials is quiet partial. Therefore, more studies of extensive period of effective lipoprotein (a) lowering therapy in high-risk persons are necessary.Places of interest the latest findings in this review article on lipoprotein (a) as a risk factor comprising a novel perception into its association, pathogenicity and mounting clinical significance in a coronary arterial disease. New prospects for lipoprotein (a) lowering interferences and elements disturbing plasma lipoprotein (a) levels will also be deliberated.

Lipoprotein (a) Structure:

Lipoprotein (a) is an unique, modified form of LDL containing an additional protein, apo(a), with similar plasminogen aminoacid arrange.Lipoprotein (a) has established to be pathophysiologic mechanisms associate a pivotal association between amplified level of circulating concentrations of Lipoprotein (a) and atherosclerotic cardiovascular disease, valvular aortic stenosis.[1]

In 1963, lipoprotein (a) was revealed, by the geneticist Kare Berg duringinventive set of immunological studies of human sera, exposed a novel antigen that was associated with low density lipoproteins (LDL) particle like Apo-lipoprotein B, associated which is one of the large glycoprotein molecule.[2]

In lipoprotein (a) the Lp denoting to the lipoprotein and in brackets the small "a" referring as for naming antigens protein linked to low density lipoprotein in human immunogenetics that was at that time knownlexicon.Apo- lipoprotein (a) is a plasminogen like, havingnumerousreplicas of plasminogen.The LPA gene is strictly linked to plasminogen from which it has developed by duplications, deletions, point mutations and by gene conversions. Plasminogen is categorized by five different paralogouskringle domains (Kringle I to V), each present as single copies and anindolent protease sphere.The kringle 4 domains can differ from 12 to 51 liberalupsurgesto 34 variable-sized apo-lipoprotein (a) isoforms.[2, 3]

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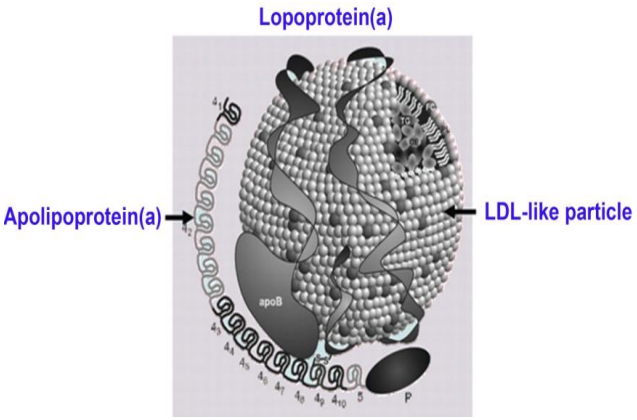

Figure No. 1Structure of Lipoprotein (a) [15]

Lipoprotein(a) Metabolism (Sally et al 2004)[5]:

Due to similarity of lipoprotein (a) with LDL could be evisceratedthrough the LDL receptor (LDLR), Earlierreadings of mutant LDLRs with familial hypercholesterolemia persons have reinforced this hypothesis by comparing control subjects with increased levels lipoprotein (a) in FH individuals. In various animal studies showed that liver with other organ like spleen and muscle is the foremost site of lipoprotein (a) metabolism. As glycoprotein receptor (ASGPR) that drags and affects lipoprotein (a) this is extremely uttered in the liver by Kostner et al. The liver manufactured and concealed lipoprotein which is derivativeof apo-lipoprotein (a) .It removed from the circulation mainly by the kidney and at small extent by the peripheral tissues.[6]

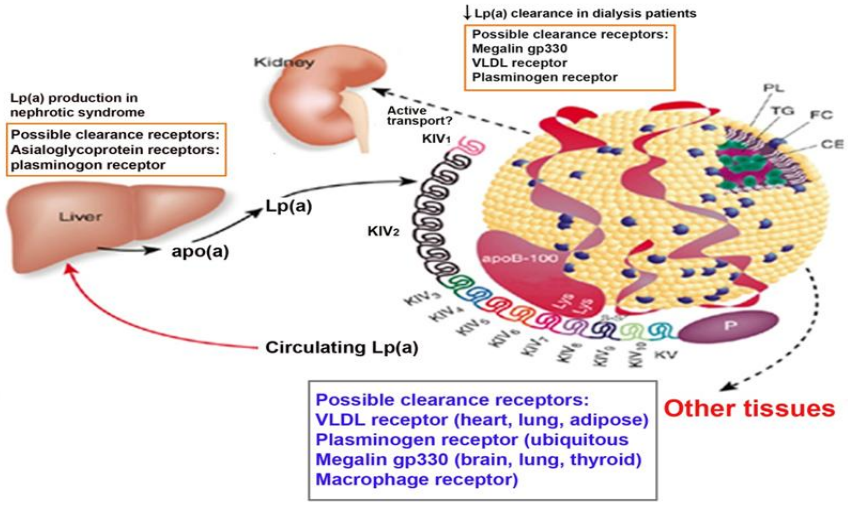

Figure No.2 Metabolism of Lipoprotein (a) [7]

Lipoprotein A and genetic influence:

Genetic influenceover the lipoprotein (a) is primarilyexercised through the LPA locus. LPA alleles areuttered co-dominantly. Gene loci on chromosome 6q other than LPA explaining an additional small fraction of the variation in lipoprotein (a) concentrations have been claimed. Additional loci identified to be associated with lipoprotein (a) levels in some

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other linkage studies include regions on chromosomes 13q22-31, 11p14-15 and 1q23 but these have not been confirmed, either. Risks of coronary arterial disease (CAD) werestrappingly allied with (6q26–27, 9p21, and 1p13)chromosomal regions. The strongest link at chromosomal region (6q26–27) between *LPA* locus and lipoprotein.[8]

The apo-lipoprotein (a) (a) size polymorphism as first discovered by Uterman which has a greatimpact on lipoprotein(a) levels, who reported an converseaffiliation between and lipoprotein (a) levels in plasma and number of KIV repeats.[3] Recent study recognized in American population a noteworthyassociation between a region on chromosome 19 andplasma lipoprotein (a) levels. This apo a lipoprotein is highly glycosylated protein analysis of apo a c-DNA merriment close homology with plasminogen,an significant component of fibrinolysis. The apo protein (a) gene (LPA) positioned on chromosome no: 6q26-27 which controlled the extremely inherited lipoprotein (a) plasma concentration in human serum.

Lipoprotein (a) as a genomicvariation of low-density lipoprotein and believed to be spread as an autosomal dominant trait. Future quantitative immunochemical studies have provided proof that the lipoprotein (a) epitomizes a quantifiableslightly than a qualitative genomicindicator and is underneathmultigenomiccontroller. Additional related study recognized a region on chromosome 1 as devising a substantial role in the families of Western Europe.[9]

Pathogenicity of lipoprotein (a):

Most of literatures have exposed an assortment of biological eventscreated by lipoprotein (a) that mightbe enlighten its character in the expansion of Coronary arterial disease (see Table 1). In the arterial wall, the accretion of lipid occurs due to fixation of triglyceride-rich lipoproteins stuff with lipoprotein (a)after subsidization.Macrophages of arterial wall take up oxidized low-density lipoproteins, which responsible for cellular accretion of cholesterol, oxysterolsand powering the development of foam cells. An oxidized low density lipoprotein like lipoprotein (a) molecule ensure inflammatory properties which responsible for the persuading of countenance of vascular adhesion molecules and chemotaxis of monocytes. Lipoprotein (a) is thrombotic in nature have provided confirmation by some human and animal studies.[10]

Table 1 Pathogenic Accomplishments of Lipoprotein (a)

Atherogenic Activity	Thrombogenic Activity
↑ Permeability of EC layer	↓ Plasminogen activation
↑ Vascular adhesion molecule expression	↑ PAI-1 expression
↑ Chemotaxis of monocytes	↓ TFPI activity
↑ Foam cell formation ↑ SMC proliferation and de-differentiation	↑ Platelet aggregation

EC, endothelial cell; SMC, smooth muscle cell; PAI-1, plasminogen activator inhibitor-1; TFPI, tissue factor pathway inhibitor.

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Lipoprotein (a) and Cardiovascular Risk: [11, 12, 13]

Severalscientific trials have revealed high plasma concentration of lipoprotein (a) to be anself-governingjeopardy to development of cardiovascular disease. Most of the studies showed that the incident of hazard of emerging CAD from theraised lipoprotein (a) plasma concentration is amplified in the existence of further lipid accretionissues such as low HDL cholesterol or high LDL cholesterol. Combination of thrombogenic risk factors such as, protein C and S deficiency, Factor V Leiden mutationprothrombin G 2021A mutation and antithrombin III deficiency are related tohigh plasma concentration of lipoprotein(a). In the arterial wall the affinity of apo-lipoprotein (a) for extracellular matrix proteins is accountable for accrual of lipoprotein (a). Hughes et al. have revealed that in extracellular matrix(ECM)the affinity of lipoprotein (a) molecule for the is intercededthroughplasminogen like lysine in apo(a), fibrin binding has been suggested to show an imperative role lipoprotein (a) accretion in the arterial wall.[14]

Type-2 DM and lipoprotein (a):

Unfamiliar plasma lipoprotein (a) is an entailing of a LDL with cholesterol-rich element with one of the molecule of apo-lipoprotein (apo) (a) extra protein covalently linked to apo-lipoprotein (apo) B-100.(Figure1).[15]In lipoprotein (a), there are two main apo-lipoproteinmolecules existingas apo-lipoprotein (a)besidesapo-lipoprotein B. The molecular weight and amino acid conformation of apo-B moiety is analogousto low-density lipoprotein of apo-B which is the foremosttransporter of cholesterol in serum. The hazard of ischemic vascular disorders isautonomously, precisely and unceasingly associated with the high plasma concentration of lipoprotein (a). Lipoprotein (a) pathogenicity mechanism has not been copiouslyexplained; nevertheless, at the sites of the atherosclerotic lesions, lipoprotein (a) is existing in the arterial wall that is wellacknowledged.[15, 16]

Risk of Cardiovascular disease and cerebrovascular disease throughanti- fibrinolytic /prothrombotic upsurge with eminent lipoprotein(a) levels can conceivably the effects as apo-lipoprotein(a) owns toplasmin and plasminogen with structural homology but has not at all fibrinolytic action and throughboosted atherogenesis as an accretion of cholesterol and lipoprotein(a) in the intima of vascular wall. In persons permitted of predominant cardiovascular disease, thelipoprotein (a) is asovereignthreatcause for intima-media carotid thickening [17]. Lipoprotein (a) seems to persuade vascular damage through causal mechanisms that includeapo (a) oxidized and isoforms phospholipids. Elevated lipoprotein (a) levels may primarily basis ofatherosclerosis rather than thrombosis[18].

Sovereign of diet, age, physical exercise, smoking habits, alcohol consumption, and sex lipoprotein (a) has been revealed to be a threat factor for atherosclerosis in adults. Obtainableproof exposed the contributory part of the particle in coronary vascular disorders. Further study is desired in addition to this in Indians to evaluate the significance of the risk factor to vascular disease in this populaces.[19]

Counter instinctivepossessions of lipoprotein (a) ontype 2 diabetic mellitus and insulinresistanceprimaryrumors have projected an converseassociationamongthe diabetes and plasma concentration of LDL- cholesterol.[20] Ananalogousreverseassociationof lipoprotein(a)

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with dysmetabolic syndrome like obesity, diabetes, and insulin resistance has been quantified in severalforthcoming studies.[21,22,23]

A study of 134,707 subjects from numerous studies monitored up for5-20 years has shown a twenty five percent lesseroccurrence of diabetes in contestantswith a low plasma concentration of lipoprotein (a) vs.high.[22]Additional, the geneticprotection contrary to type 2 diabetic is abridged with very stumpylipoprotein (a) <5 mg/dland/or hugeLp (a) isoforms (projected to be establish in ten percent ofthe biosphere'spopulace).[22,23]The occurrence of either onetype 2 diabetic or high lipoprotein(a) is related with atwo to three times threat of coronary arterial disease compared to individualsdeprived of suchsituations.[24,25]Thoughcertainanalyses have revealed an relationshipof raised lipoprotein (a) concentration with sophisticated threat and cruelty of coronary arterial disease inpatients with type 2 diabetic mellitus,[26]other literatures have revealed a inconsistentlylower jeopardy of coronary arterial disease in patients who have in cooperation with theeminent lipoprotein (a) andtype 2 DM.[22,27,28]Prospective studies, the subject of 2308 women and men with twelve year follow-up in type 2 DM lipoprotein (a) genetic score and plasma concentration of lipoprotein (a) were not related occurrence and death with cerebrovascular disease.[28] To focus on a powerful research how to amplified lipoprotein (a) defends in contrast to type 2 DM, while hastening atherothrombosis, has changed now. In metabolic syndrome such heterogeneity is associated with the raised lipoprotein (a) level.

Diabetes and Stroke:

Carotid artery disease is a vital avoidable risk factor for stroke, which is a leading to mortality and long-term disability. Several studies have established higher Lipoprotein (a) level to be a strong threat factor for the occurrence and cruelty of cerebrovascular disease and premature stroke in diverse populations. A case control study of fifty middle age and sex matched control subjects and fifty patients aged <40 years with ischemic stroke established higher lipoprotein (a) is to be the only threataspect that was ominously higher in patientsvs. controls.[29] Predictors of ischemic stroke,apo-B and apo-A ratio and lipoprotein (a) in additional studies had been revealed.[30] In Indian for stroke, lipoprotein (a)high level is also correlated with amplified harshness and subordinate long-term prediction.[30] conjointly in Indians, various studies demonstration that lipoprotein (a) is an important initial source and progressive atherosclerosis and ischemic stroke.[29,32]

Asian Indian and Non-Hispanic Whites men have elevated lipoprotein (a) level than Chinese men, with identical associations in women. Higher lipoprotein (a) may be sturdily related with ischemic heart disease in Asian Indians and Chinese.[33,34]. High lipoprotein (a) concentration is an autonomous threat factor for acute myocardial infarction in assorted populations demonstrated by this persuasively.Raisedconcentration of lipoprotein (a) in serum had more in South Asian than the whites[35]. Study of African Americans on this portent is corresponding to the three times greater risk of stroke from hypertension than in whites.[36]Dyslipidemia of South Asian population characterizedby the low density lipoprotein particles that are vastlyaugmented with lipoprotein(a) andapo- lipoprotein B couldafford a probableclarification for the discriminating risk ofcoronary arterial disease.[37,38,39]South Asians have higher apo B and apo A ratio than whites, despite having a lower total

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cholesterol level [39,40], In another study in acute myocardial infarction as an interpreter this ratio is greater than the lipid profile findings.[39,41]In a medical perception in South Asians population, the fact to finding here is that total cholesterol level and LDL-C may distinctly miscalculate coronary arterial disease risk Moreover, the high density lipoprotein particles are washed-out of apoA1 and provide little safety.[40, 42] Lipoprotein (a) concentration compare inversely with insulin levels in type 2 diabetic individuals which may be exclusive threat factor of the cardiovascular disorders in type 2 diabetic patients with longer duration of diabetic mellitus.[43] Heffner et al proposed that the association between insulin sensivity and lipoprotein level (a) might be reliant on genes for apo (a) genotype could be relation imbalance.[44]Psyogiannis et al demonstrated that lipoprotein (a) level significantly increased in offspring of type 2 diabetic patients apart from insulin sensivity.[45]In South Indian population plasma lipoprotein (a) concentration is an independent risk factor for coronary arterial disease in NIDDM patients.[46]Guillaume Pare et al(2019) evaluatedvariations in lipoprotein(a) level and isoform sizes across multiple ethnic groups noted that the risk of myocardial infarction amplified with high lipoprotein (a) plasma concentrations, independent of lipoprotein (a) isoform size in all populations specially including the South Asian and Latin American populations than the Arabs and Africans.[47,48]Ashfaq F et al did a cross sectional study on North Indian population with 360 subjectsin which they found that association between lipoprotein (a) level and severe pattern of coronary atherosclerosis disease and confirms the usefulness of lipoprotein (a) and other risk factors, particularly in normolipidemic individuals and also notedrelation of higher level of triglyceride strongly associated with greater extent of atherosclerosis may designate multiple-vessel involvement and probably needs close clinical surveillance .[49]Lipoprotein (a) level are self-reliantlyassociated to carotid artery disease particularly intimal medial thickness of arterial wall in Type 2 diabetic patients which have been established by most of the devastating studies of south Indian population,demonstrating an significant role of lipoprotein (a) in initial atherosclerosis.[52-53.]Other related studies havebeen reported by Bittner et al[54], Goodman et al [55] and Szarek et al[56].

CONCLUSIONS:

Eras of study on lipoprotein (a) ought to tacit itmaterialize as a clinically imperativeparticle. Indication for lipoprotein(a)engrossment in the progress of coronary heart disease to anargumentwhere tediousamount of lipoprotein (a) in persons at risk must be endorsed.Ample of evidence has beenaddedconcerning the metabolism genomic influences, and biological action of lipoprotein (a); still, certainqueriescontinue in relation to its association, catabolism and exchanges with additionaljeopardyelements. In this review on the basis of recent available literature we deliberate the pathophysiologicalrole and clinical significance of lipoprotein (a) regarding the development of coronary vascular disease, stroke, other metabolic and vascular disease.The development of a therapeutic agent is aunique foremostcontest that quietleftovers,precisely lowering plasma concentration of thelipoprotein (a). Lipoprotein (a) levels would be reflected in specifically in middle age with a family history of diabetes or high blood cholesterol levels. Regrettably, at present have been insufficient studies to determine which therapies might be helpful. The developmentofsafe and activeproceedsto pull downplasma concentration of lipoprotein (a) in will convey the

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incidence to conduct interference trials to moreinterpretconsequences of lipoprotein (a)in advancement of coronary vasculardisease.

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