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Lipoprotein (A) As a Risk Factor in Myocardial Infarction

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Abstract: **Myocardial infarction (MI) remains a leading cause of morbidity and death regardless of targeting of low-density lipoprotein (LDL) cholesterol by statin treatment. The requirement for recognition of extra causal factors. We aimed by this comprehensive review to discuss the role of lipoprotein (A) as a risk factor of the most devastating ischemic heart disease which is myocardial infarction. We Conducted a database; PubMed and Embase comprehensive search up to December 2016, we search a relevant trail to our concern topic (Role of Lipoprotein (a) as risk factor of cardiovascular diseases, myocardial infarction). The occurrence of elevated serum Lp(a) level was not significantly different in between patients with myocardial infarction and control subjects, recommending that this lipoprotein might not play a crucial role in the pathogenesis of ischemic heart diseases. Numerous studie showed a significantly greater level of serum Lp(a) was noted in patients with, than in those without, prior MI, recommending that Lp(a) is a risk factor for the occurrence of AMI. Raised Lp(a) levels might promote atherosclerosis via Lp(a)-obtained cholesterol entrapment in the intima, through inflammatory cell recruitment, and/or by means of the binding of pro-inflammatory-oxidized phospholipids.**

Keywords: **Myocardial infarction (MI), low-density lipoprotein (LDL).**

1. INTRODUCTION

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide [(1)]. Regardless of global reductions in age standardized incidence of acute myocardial infarction (MI) and in the occurrence of angina given that the early 1990s, growing populations of aging high-risk people led to a boost in the worldwide problem of IHD [(2)]. Over the last 30 years, development of innovative coronary care, execution of early reperfusion strategies, and introduction of new pharmacologic techniques have actually added to a 60% reduction in death during the first 30 days after intense MI [(3)]. However, improved survival during the intense event led to growth of the pool of patients at risk for advancement of cardiac arrest [(4)]. Epidemiologic research studies have actually suggested that in recent decades an increased occurrence of postinfarction cardiac arrest parallels the reducing acute death rates [(3)].

Lipoprotein(a) is a plasma lipoprotein consisting of a cholesterol-rich LDL particle with one molecule of apolipoprotein B100 and an additional protein, apolipoprotein (a), attached through a disulfide bond (**Figure 1**) [(5)]. Elevated Lp (a) levels can potentially increase the risk of CVD (i) by means of prothrombotic/anti-fibrinolytic results as apolipoprotein(a) has structural homology with plasminogen and plasmin but has no fibrinolytic activity and (ii) by means of sped up atherogenesis as a result of intimal deposition of Lp(a) cholesterol, or both. Lipoprotein(a) [Lp(a)] has been considered a cardiovascular risk factor for many years [(5)]. Owing to incomplete scientific evidence, screening for and treatment of high Lp(a) levels need to date been performed mainly by lipid professionals. However, during the last couple of years, major advances have actually been attained in comprehending the causal function of raised Lp(a) in premature cardiovascular disease (CVD) [(6,7,8)].

A lot of scientific trials research study examining the effects of cholesterol decreasing medications on the prevention of cardiovascular disease (CVD) have actually focused on low density lipoprotein cholesterol (LDL-C). Elevated serum level of lipoprotein (a) (Lp(a)), an LDL particle linked to the plasminogen-like glycoprotein, has actually been an independent risk factor for atherosclerotic CVD, especially in those with high low-density lipoprotein cholesterol (LDL-

C) or non- high-density lipoprotein cholesterol (HDL-C) [9,10]. Results of Lp(a) on vasculature are not totally understood. Animal and human research studies have actually shown that Lp(a) can enter intima of arteries [11]. Thus, it may have a role in inflammation of foam, thrombosis, and intima cell development; all these procedures are associated with advancement of atherosclerosis [12,13]. It is approximated that around 1.5 billion people have Lp(a) levels greater than 500 mg/L [14]. Lp(a) levels are, to a large level genetically determined, stable are not substantially influenced by diet plan, workout, or other environmental factors [15].

We aimed by this comprehensive review to discuss the role of lipoprotein (A) as a risk factor of the most devastating ischemic heart disease which is myocardial infarction, we also intend to examine the correlation between the lipoprotein (a) and cardiovascular disease and mostly MI.

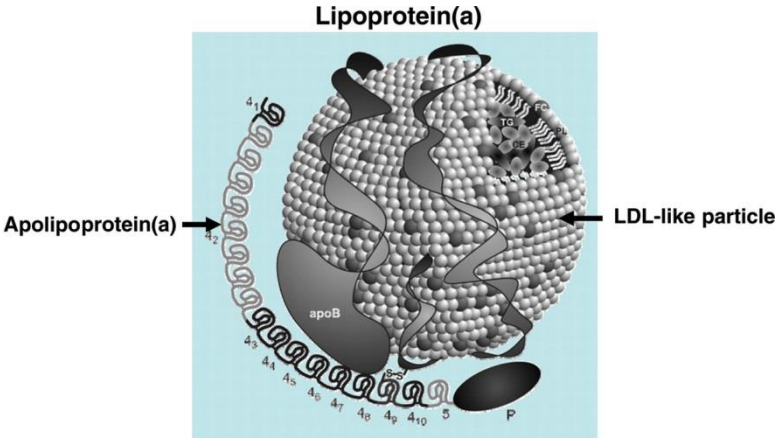

Figure 1: Lipoprotein(a) consists of an LDL-like particle to which apolipoprotein(a) is covalently linked. The LDL-like moiety is composed of a central core of cholesteryl esters (CE) and triglycerides (TG) surrounded by phospholipids (PL), free cholesterol (FC), and a single molecule of apolipoprotein B (apoB). Apolipoprotein(a) contains 10 different types of plasminogen kringle 4-like repeats as well as regions homologous to the kringle 5 and protease (P) regions of plasminogen. [5]

2. METHODOLOGY

We Conducted a database; PubMed and Embase comprehensive search up to December 2016, we search a relevant trail to our concern topic (Role of Lipoprotein (a) as risk factor of cardiovascular diseases, myocardial infarction); using following Mesh words:

- acute myocardial infarction;
- apo(a), apolipoprotein(a);
- HDL, high-density lipoprotein;
- LDL, low-density lipoprotein;
- Lp(a), lipoprotein(a);
- MI, myocardial infarction;

To identify the most related articles in the literature and to performed more supported evidence based review. We also scanned the references list of each identified articles for more relevant studies, our search was restricted to English language articles and only human subjected studies.

3. RESULTS & DISCUSSION

Myocardial infarction (MI) remains a leading cause of morbidity and death regardless of targeting of low-density lipoprotein (LDL) cholesterol by statin treatment. The requirement for recognition of extra causal factors, and hence prospective new targets for prophylactic treatment, appears. Elevated levels of lipoprotein(a) represent such a candidate [15,16,17]; however, whether lipoprotein(a) causes MI is uncertain. A randomized intervention trial revealing that a decrease in lipoprotein(a) levels causes a decrease in risk of MI would favor causality. Such a study has yet to be performed. Additionally, a mendelian randomization study can likewise provide evidence of causal relationships making money from population circulations of risk alleles that are typically independent of behavioral and environmental factors, thus yielding

largely unconfounded risk associations and leaving out associations caused by reverse causation [18,19]. Put simply, association of elevated levels of lipoprotein (a), along with association of genetic variation raising levels of lipoprotein(a), with risk of MI would suggest causality.

- **Overview of Epidemiology studies:**

Findings from earlier potential studies recommend that the relation between Lp(a) concentration and the risk of CVD may involve a limit which the association might be more marked amongst individuals with raised LDL cholesterol [20,21,22]. Specific research studies, however, are seldom adequately powered to evaluate the shape of the relation or to make accurate estimates of relative risk within subgroups of the study populations such as amongst individuals with high instead of low LDL cholesterol levels.

An early meta-analysis [23] of 18 potential studies of basic populations that was released prior to 2000, which reported on a pooled analysis of 4000 coronary cardiovascular disease (CHD) cases, recommended that the combined relative risk of CHD for individuals in the top vs. bottom thirds of standard Lp(a) concentrations was 1.7 (95% CI: 1.4-1.9) [23]. An updated meta-analysis of 31 potential studies, involving an overall of 9870 CHD cases, recommended that the matching combined risk was more modest (relative risk: 1.5; 1.3-- 1.8) (24). Subgroups defined by other characteristics pre-specified for investigation, especially study size, sample storage attributes, and Lp(a) assay isoform level of sensitivity, were not substantially different.

Although the proof from literature-based meta-analyses of prospective studies suggests the possible value of Lp(a) in CHD, it does not provide adequate detail to allow the evaluation of the relevance of this lipoprotein to CVD prevention and treatment. It is not possible to determine, from a literature-based meta-analysis, whether Lp(a) is associated with CHD throughout the concentration variety (similar to blood pressure and LDL cholesterol) or whether Lp(a) is particularly atherothrombogenic in particular subgroups of individuals (such as in those with high LDL cholesterol level) [23].

- **Genetics roles in Lp (a) mechanisms:**

Plasma levels of Lp(a) are to a big degree genetically determined via variation in the apolipoprotein(a) gene [5]. This makes the apolipoprotein(a) gene ideal for usage in a Mendelian randomization study, [25] examining whether long-lasting, genetically elevated levels of plasma Lp(a) cause CVD. By analogy, familial hypercholesterolaemia with anomalies in the LDL receptor or apolipoprotein B genes have lifelong, genetically elevated LDL cholesterol levels and early CVD, [26,27] a reality that has actually assisted develop that elevated LDL cholesterol levels make up a direct cause of atherosclerosis and CVD.

A Mendelian randomization study needs 3 pieces of data to assist offer proof for a causal link between elevated plasma Lp(a) levels and CVD [25]. Initially, raised plasma Lp(a) levels should be related to increased CVD risk, as demonstrated in the previous section on Lp(a) epidemiology. Second of all, hereditary variation needs to exist in human populations that can discuss a big portion of the variation in plasma Lp(a) levels: such hereditary variation has been known for many years, most importantly the kringle IV type 2 size polymorphism (**Figure 1**), leading to a variable number from 2 to > 40 number of a 5.6 kb repeat associated inversely with plasma Lp(a) levels. Hence, the less the repeats in the apolipoprotein(a) gene, the greater the plasma levels of Lp(a), which has also been shown in the past [5]. Such genetic variation ought to be connected directly with CVD risk: previous smaller sized case- control studies (n < 2400) have demonstrated an association of kringle IV type 2 genotype [or the associated apolipoprotein(a) isoform size] with risk of CVD, as reviewed formerly [5,6].

On the basis of the Copenhagen City Heart Study (CCHS), the Copenhagen General Population Study (CGPS), and the Copenhagen Ischemic Heart Disease Study (CIHDS) with 40 000 people genotyped for the kringle IV type 2 size polymorphism in the apolipoprotein(a) gene, a large Mendelian randomization research study was published in 2009 [6]. In the CCHS, multifactorially changed danger ratios for myocardial infarction for raised lipoprotein(a) levels were 1.2 (95% CI: 0.9- 1.6) for the 22nd-- 66th percentile, 1.6 (1.1-2.2) for the 67th-- 89th percentile, 1.9 (1.2- 3.0) for the 90th-- 95th percentile, and 2.6 (1.6-- 4.1) for levels > 95th percentile, respectively, vs. levels <22nd percentile (pattern P< 0.001; Figure 2) [6].

- **Pathophysiological the atherothrombotic based on of lipoprotein(a):**

After transfer from plasma into the arterial intima, Lp(a) may be more avidly maintained than LDL as it binds to the extracellular matrix not just through apolipoprotein(a), however likewise by means of its apolipoprotein B component, [28] therefore contributing cholesterol to the expanding atherosclerotic plaque. In vitro, Lp(a) binds to several extracellular matrix proteins consisting of fibrin [29] and defensins, a family of 29- 35 amino acid peptides that are released by

neutrophils during inflammation and severe infection [30]. It is most likely that defensins, like lipoprotein lipase, provide a bridge between Lp(a) and the extracellular matrix.

Transgenic mice expressing a mutant kind of apolipoprotein(a) with considerably reduced capability to bind to fibrin showed 20% less atherosclerotic sore area and less build-up in the arterial wall compared with transgenic mice revealing wild-type Lp(a) [31]. In addition, Lp(a) appears to be maintained at sites of mechanical injury; [28] fibrin deposition takes place preferentially at such sites.

Through its apolipoprotein(a) moiety, Lp(a) also connects with the β2-integrin Mac-1, consequently promoting the adhesion of monocytes and their transendothelial migration [32]. In atherosclerotic coronary arteries, Lp(a) was discovered to localize in close proximity to Mac-1 on infiltrating mononuclear cells.

Lipoprotein(a) has likewise been shown to bind pro-inflammatory-oxidized phospholipids (33)and is a preferential provider of oxidized phospholipids in human plasma. Lipoprotein(a) also contains lipoprotein-associated phospholipase A2 (similarly referred to as Paf-acetylhydrolase), which may cleave oxidized fats at the sn-2 position in oxidized phospholipids to yield short chain fatty acids and lysolecithin [34].

Apolipoprotein(a), a homologue of the fibrinolytic proenzyme plasminogen, hinders fibrinolysis [35]. Lp(a)/ apolipoprotein (a) can competitively prevent tissue-type plasminogen activator-mediated plasminogen activation on fibrin surface areas, although the system of inhibition by apolipoprotein(a) remains questionable. Necessary to fibrin embolisms lysis are a variety of plasmin-dependent, favorable feedback responses that enhance the effectiveness of plasminogen activation, consisting of the plasmin-mediated conversion of Glu-plasminogen to Lys-plasminogen. It has actually been observed that the apolipoprotein(a) part of Lp(a) prevents the crucial favorable feedback action involving conversion of plasmin-mediated Glu-plasminogen to Lys-plasminogen [36]. Lipoprotein(a) might likewise improve coagulation by preventing the function of tissue factor pathway inhibitor [37].

Little isoforms of apolipoprotein(a) have actually been observed to possess raised effectiveness in inhibiting fibrinolysis and thereby promoting apoplexy [38]. A current meta-analysis demonstrated a two-fold increase in the risk of CHD and ischaemic stroke in topics with little apolipoprotein(a) phenotypes [39]. Prospective findings in the Bruneck study have actually revealed a considerable association particularly between small apolipoprotein(a) phenotypes and advanced atherosclerotic disease involving a part of plaque thrombosis [40]. These data suggest that the decision of apolipoprotein(a) phenotype/genotype might offer clinicians with extra information by which to assess Lp(a)/ apolipoprotein(a)-associated atherothrombotic risk.

- **MI in patients with high Lp(a) levels:**

In accordance with previous findings, [5] raised lipoprotein(a) levels were related to increased risk of MI (Figure 2) (pattern, P <.001), with multivariable-adjusted HRs of 1.2 (95% CI, 0.9-1.6; events/10 000 person-years, 59) for levels between the 22nd and 66th percentile, 1.6 (95% CI, 1.1-2.2; events/10 000 person-years, 75) for levels in between the 67th and 89th percentile, 1.9 (95% CI, 1.2-3.0; events/10 000 person-years, 84) for levels between the 90th and 95th percentile, and 2.6 (95% CI, 1.6-4.1; events/10 000 person-years, 108) for levels greater than the 95th percentile, respectively, vs levels less than the 22nd percentile (events/10 000 person-years, 55). On extra change for the KIV-2 genotype, HRs were attenuated (Figure 2). No considerable interactions were observed between lipoprotein(a) levels and age, sex, overall cholesterol (fixed for the lipoprotein [a] contribution), triglycerides, body mass index, high blood pressure, diabetes mellitus, smoking, lipid-lowering therapy, menopause, or use of hormone treatment on risk of MI in the CCHS (P values of.16 to.97 for tests of interaction) [5].

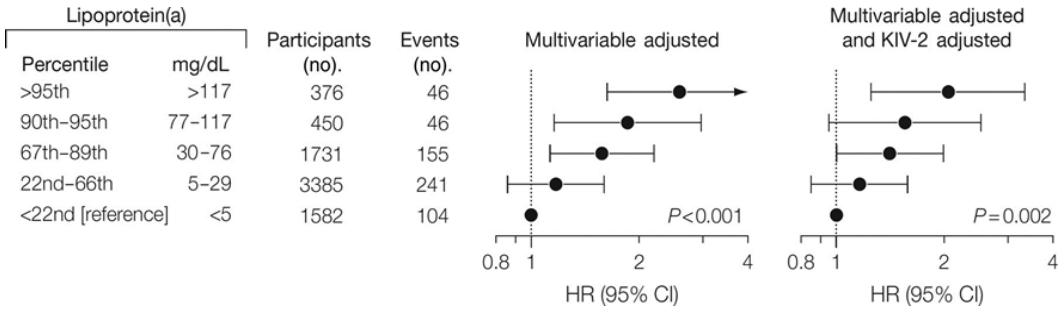

Figure2: Risk of myocardial infarction by levels of lipoprotein(a) in the general population. Hazard ratios (HRs) are adjusted for cardiovascular risk factors (multivariable) or for these factors as well as kringle IV type 2 (KIV-2) genotype. P-values are test for trend of hazard ratios where lipoprotein(a) groups with increasing levels were coded 1, 2, 3, 4, and 5. (5)

4. CONCLUSION

The occurrence of elevated serum Lp(a) level was not significantly different in between patients with myocardial infarction and control subjects, recommending that this lipoprotein might not play a crucial role in the pathogenesis of ischemic heart diseases. Numerous studie showed a significantly greater level of serum Lp(a) was noted in patients with, than in those without, prior MI, recommending that Lp(a) is a risk factor for the occurrence of AMI. Raised Lp(a) levels might promote atherosclerosis via Lp(a)-obtained cholesterol entrapment in the intima, through inflammatory cell recruitment, and/or by means of the binding of pro-inflammatory-oxidized phospholipids. The prothrombotic, anti-fibrinolytic actions of apolipoprotein(a) are revealed on the one hand as inhibition of fibrinolysis with improvement of embolisms stabilization and on the other as improved coagulation via the inhibition of tissue factor path inhibitor.

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