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Lipoprotein(a) Oxidation, Autoimmune and Atherosclerosis

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1. Introduction

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein whose structure and composition closely resembles that of low density lipoprotein (LDL), but with one of additional molecule of apolipoprotein(a) [apo(a)], a large glycoprotein linked to apoB by a disulfide bond (Figure 1) [1, 2]. High Lp(a) levels have been established as an independent risk factor for atherocslerosis [3-5], and Lp(a) deposits have been found in atherosclerotic lesions but not in normal arterial walls [6-8].

Lp(a) can be modified by oxidation *in vitro*, and then be taken up by macrophages by means of scavenger receptors, where it promotes their transformation into foam cells within the arterial walls [9-13]. Oxidized Lp(a) [ox-Lp(a)] may also induce adhesion molecular expression on monocytes, promoting their recruitment and adhesion to the endothelium [14], and influence the responsiveness of platelets to various agonists [15]. Modified forms of Lp(a), some resembling oxidized Lp(a), have been identified in human atheromatous lesions [16]. In addition, ox-Lp(a) causes significant changes in apo(a) conformation, which could enhance the interaction of these particles with plasminogen binding sites as well as macrophage scavenger receptors, resulting in increased inhibitory effect on plasminogen activation and finally leading to attenuate fibrinolytic activity [17].

Ox-Lp(a) has been reported to play more potent role than native Lp(a) in atherosclerosis [10, 14, 17, 18], and autoantibodies against ox-Lp(a), Lp(a) immune complexes [Lp(a)-IC] have also been detected *in vivo* simultaneously [19, 20]. The present review article focuses specifically on the relationship between Lp(a) oxidation, autoimmune and atherosclerosis together with our recent work.

2. The pathogenic role of oxidized Lp(a)

Lp(a) contains a large specific glycoprotein called apo(a), attached by a single disulfide bridge to $apoB_{100}$ of LDL (Figure 1). The adverse cardiovascular qualities of Lp(a) have been related to both its LDL-like properties (i.e., formation of foam cells) and its presumed role in fibrinolysis.

3. Lp(a) oxidation

The structure, fatty acid composition, and antioxidant concentrations of Lp(a) and LDL are quite similar [21]. *In vitro* studies have shown that Lp(a) can be modified by oxidation (both chemical and cellular-mediated) in a fashion similar to LDL [22]. This modification, which involved lipid peroxidation measured as thiobarbituric acid-reactive substances (TBARS), caused marked changes in the structure and biological properties of Lp(a). Relative to native Lp(a), oxidized particles showed decreases of free amino groups and protein fragmentation, increased negative charge, and high aggregation ability. They were taken up and degraded readily by human monocyte/macrophages by means of scavenger receptors, a known pathway for clearance of ox-LDL in atheroma, inducing cholesteryl ester accumulation and promoting their transformation into foam cells within the arterial walls [9-13]. Similar to above-mentioned pathway, ox-Lp(a) might, in part, form aggregation and contribute to foam cell formation by additional macrophage uptake mechanism, like phagocytosis [9]. Ox-Lp(a) may also induce adhesion molecular expression on monocytes, promoting their recruitment and adhesion to the endothelium and stimulating intimal monocytes to differentiate into resident macrophages [14]. Moreover, subsequent to the induction of oxygen-derived radicals, oxidized Lp(a) may impair endothelium-dependent vasodilation [23].

4. Lp(a) and fibrinolysis

Besides above atherogenic potential, ox-Lp(a) might favor an impaired fibrinolytic activity as it has been shown through its inhibitory effect on plasminogen binding to monocyte-like cells and the induction of plasminogen activator inhibitor-1 (PAI-1) overproduction in cultured human umbilical vein endothelial cell. Several plausible mechanisms were proposed to explain the anti-fibrinolytic potential of Lp(a) [24]. A considerable part of the anti-fibrinolytic properties of apo(a) seemed to reside in its molecular similarity to plasminogen [25]. Lp(a) inhibited plasminogen binding and activation at the surface of stabilized fibrin, endothelial cells and platelets in a dose-dependent fashion [25].

Oxidative modification of Lp(a) causes significant changes in apo(a) conformation, resulting in enhanced interaction of these particles with plasminogen binding sites and macrophage scavenger receptors [17]. These findings were supported by some clinical studies. Pepin et al. [8] found that Lp(a) in atherosclerotic lesions was oxidized, and the oxidized Lp(a) could be a more tightly bound fraction than apoB. Two studies reported large variations in the lysine binding capacity of Lp(a) purified from different individuals [26, 27]. This heterogeneity appeared not to be associated with apo(a) isoforms. Wang et al. [28] developed an enzyme-linked sandwich immunosorbent assay (ELISA) to determine Lp(a)-associated plasminogen epitopes. The Lp(a)-associated plasminogen epitopes levels and this plasminogen epitopes to Lp(a) ratio have been found significantly increased in patients with hemodialysis, which may also be caused by the oxidative modification of Lp(a). In addition, Lp(a), especially in oxidized form, increases over two-fold the endothelial synthesis and secretion of PAI-1 *in vitro*, especially for the 2/2 PAI-1 genotype [29, 30].

5. Oxidized Lp(a) *in vivo* and autoantibody

The role of autoimmune-mediated pathways in the development of atherosclerosis has been the focus of much interest. Circulating ox-LDL and malondialdehyde (MDA) modified LDL

(MDA-LDL) have been reported to be useful markers for identifying coronary artery disease (CAD) [31-33]. Some studies support the relationship of increased levels of antibodies to ox-LDL with the severity of atherosclerosis and future development of myocardial infraction [34], although the pathogenic role of these antibodies in atherosclerosis is controversial.

Similarly, there is evidence supporting the presence of ox-Lp(a) *in vivo*. Thus, modified forms of Lp(a), some resembling ox-Lp(a) and some possibly degraded, have been identified in extracts of human advanced atherosclerotic plaques [16]. Romero et al. [35] reported the existence of autoantibodies against MDA-Lp(a) *in vivo*. Their study found the fact that most anti-MDA-Lp(a) also react against MDA-LDL and suggested the involvement of a common epitope in the reactivity of the majority of antibodies against these oxidatively modified lipoproteins, which might be caused by the existence of antibodies against modified apoB. While some patients were found seropositive for only one or the other autoantibodies against LDL or Lp(a), which supported the hypothesis of the existence of a separate antibody, which might be antibodies against modified apo(a).

Wang et al. [36] have isolated and identified the ox-Lp(a) autoantibodies by an affinity chromatographic column of Sepharose 4B coupled with ox-Lp(a) from healthy subjects. All the isolated antibodies, after being fully absorbed by the ox-LDL column, showed different low reactivity with ox-LDL, while some of them still appeared high reactivity with ox-Lp(a), which suggested that autoantibody against ox-apo(a) exist *in vivo* and the isolated human autoantibodies against ox-Lp(a), which can recognize both apo(a) and apoB epitopes of ox-Lp(a).

6. Oxidized Lp(a) assay

Apo(a) and apoB proteins of Lp(a) molecule can both be oxidatively modified *in vivo*. The degree of oxidized apo(a) or apoB protein of Lp(a) has been detected to estimate circulating ox-Lp(a) levels [37-40]. Yamada et al. [37] obtained a new 161E2 monoclonal antibody to react with oxidized Lp(a) but not with native Lp(a). The 161E2 monoclonal antibody was produced against synthetic peptide antigen, which was characterized as having various properties because its external exposure was induced as a result of oxidative modification. Using this antibody, they developed a ELISA to measure Lp(a) modified by oxidative stress, and found that hypertensive patients with complications showed a significantly higher level of oxidized Lp(a) in serum than did normotensive subjects, whereas there was no significant difference in native Lp(a) between normotensive and hypertensive subjects. Morishita R et al. [38] reported that ox-Lp(a) level in CAD patients with diabetes mellitus was significantly higher than in healthy volunteers. Moreover, serum ox-Lp(a) concentration showed a significant positive correlation with pulse wave velocity, an index of arteriosclerosis . Of importance, the deposition of oxidized Lp(a) was readily detected in calcified areas of coronary arteries in patients with myocardial infarction.

Podrez et al. [39] also found that oxidized apoB protein of plasma Lp(a) was a characteristic of the patients with end-stage renal disease undergoing continuous ambulatory peritoneal dialysis. Interestingly, from apolipoprotein E-receptor deficient mice, Tsimikas et al. [40] cloned the natural murine monoclonal IgM autoantibody E06, which could bind the cell-wall polysaccharide and prevent the uptake of oxidized LDL and apoptotic cells by scavenger receptors of macrophages. The plasma oxidized phospholipid was measured with

the use of the murine monoclonal antibody E06, and the result showed that oxidized phospholipids presented on particles of apo B-100 and primarily on Lp(a) lipoprotein correlated with both the presence and extent of angiographically documented coronary artery disease. However, neither of the above methods can simultaneously detect apo(a) and apoB epitopes of ox-Lp(a).

Wang et al. [36] developed 2 "sandwich" ELISAs for measuring plasma ox-Lp(a) level, using human autoantibodies against ox-Lp(a) to capture ox-Lp(a) or polyclonal antibodies against ox-LDL to capture oxidized apoB of Lp(a), and then quantitating with monoclonal anti-apo(a) enzyme conjugate, respectively. A significantly positive relationship was found between ox-Lp(a) levels detected by 2 ELISAs. Compared to control, plasma ox-Lp(a) levels in patients with CAD detected by 2 ELISAs were both significantly increased.

7. The clinical value of circulating oxidized Lp(a)

The mean levels of Lp(a), ox-Lp(a) and Lp(a)-IC were found much lower in newborns than in children and increased rapidly to that in children after birth. No difference of their levels was found in each of the 13 year groups in the children (Figure 2) [41]. The fact that ox-Lp(a) and Lp(a)-IC were present in all the healthy children and especially in newborns was also supported by other studies [42-44], and anti-ox-LDL antibodies and LDL-IC were also easily detectable in asymptomatic young adults and children [45, 46], suggesting that the immune response to modified lipoproteins could appear very early in the process, perhaps play an initiating role in atherosclerotic process.

It is reported that ox-Lp(a) concentrations increased in CAD patients [36] and in rheumatoid arthritis patients with excessive cardiovascular events [47]. Moreover, the concentration of serum apo(a) epitope of ox-Lp(a) was reported to be significantly increased in hypertensive patients with complications and CAD patients with diabetes mellitus [37, 38]. ApoB protein of plasma Lp(a) was also found oxidized and was a characteristic of the patients with end-stage renal disease undergoing continuous ambulatory peritoneal dialysis [39]. Thus, it is noteworthy to investigate the causal role of ox-Lp(a) in atherosclerotic cardiovascular disease in a prospective study and to explore the exact pathogenic role of ox-Lp(a).

Several studies have found that ox-Lp(a) concentrations increased in both the ACS and stable CAD patients [48-50]. Interestingly, ox-Lp(a) concentrations and the ratios of ox-Lp(a)/Lp(a) were significantly higher in the ACS patients than those in the stable CAD patients as well as control, while they remained similar between the stable CAD and control, which suggested that the increased ox-Lp(a) concentrations might mainly be attributable to the occurrence of ACS. Furthermore, ox-Lp(a) levels were found to be associated with a graded increase in the extent of CAD in the patients with ACS, while not in the stable CAD [48]. In addition, Wang et al. [49] have evaluated clinical value of ox-Lp(a) levels detected by the 2 assays for measuring plasma ox-Lp(a) level using autoantibody against ox-Lp(a) [ox-Lp(a)1] or ox-LDL [ox-Lp(a)2] in ACS and stable CAD patients. A significantly positive relationship was found between ox-Lp(a) levels detected by 2 assays. Receiver-operating characteristic (ROC) curve analysis (Figure 3) confirmed that the performance of the association of ox-Lp(a) 1 with ACS was significantly superior to those of ox-Lp(a)2, Lp(a) and LDL cholesterol; while the performances of ox-Lp(a)2, Lp(a) and LDL cholesterol with ACS were similar. The performance of the association between ox-Lp(a)1 and stable CAD

was also significantly superior to that between ox-Lp(a)2 and stable CAD. The ox-Lp(a) levels increased in CAD, especially in ACS, and might be one of the major contributing factors for the development of atherosclerosis. In addition, the autoantibody was isolated from human mix serum and can recognize both apo(a) and apoB epitopes of ox-Lp(a), the developed ELISA for ox-Lp(a) by using autoantibody may more accurately reflect the state of Lp(a) oxidation *in vivo*. It is concluded that ox-Lp(a) levels using antibodies against ox-Lp(a) might represent a better biochemical risk marker than those using antibodies against ox-LDL for ACS and stable CAD.

Wang et al. [50] have also studied plasma levels of Lp(a) and several ox-Lp(a) markers immediately before and serially up to 6 months after percutaneous coronary intervention (PCI). PCI resulted in acute elevations of native, oxidized Lp(a) and Lp(a)-IC levels in both ACS and stable CAD patients, and decrease of ox-Lp(a)-Ab (Figure 4). Interestingly, the change of ox-Lp(a) during PCI was found to correlate with the extent of angiographically documented disease only in ACS patients, while not in stable CAD. Tsimikas et al. [51] also reported that indirect and direct plasma markers of oxidized phospholipids (ox-PL) showed significant temporal elevations following ACS, but not in patients with stable CAD or in subjects without CAD. These observations indicate one possibility that ACS episode causes sustained rise of ox-Lp(a), and further support the hypothesis that ox-Lp(a) is present in ruptured or permeable plaques and is released into the circulation by PCI.

The above results are also supported by the studies about ox-PL, which have demonstrated convincingly that a key ox-PL is preferentially associated with Lp(a) [52] and correlates with both the presence and extent of angiographically documented CAD [40, 53], and their concentrations increase after ACS [51] and immediately after PCI [54].

8. The source of plasma ox-Lp(a)

Oxidized lipoprotein results from exposure of lipoprotein to oxidizing species, such as superoxide anion and hydrogen peroxide derived from all cells present in the artery wall, particularly macrophages, as well as enzymes such as lipoxygenases and products of myeloperoxidase, resulting in oxidation of the lipid and protein components [55].

The source of plasma ox-Lp(a) is unknown. Holvoet et al. [56] isolated ox-LDL from the plasma of patients with post-transplant CAD and analyzed its characteristics, which suggested that it did not originate from extensive metal ion-induced oxidation of LDL but that it might be generated by cell-associated oxidative enzymatic activity in the arterial wall. It was also demonstrated in animal models that the oxidation of LDL indeed occurs in the arterial wall and not in the blood [57].

Studies have shown that increased ox-Lp(a) level in stable CAD and especially in ACS is associate with the severity of angiographically documented disease in ACS, while not in stable CAD [48, 49]. Similarly, the extent of CAD was found related with the change of ox-Lp(a) levels before and after PCI in the ACS and stable CAD patients [50]. These above results suggested that ox-Lp(a) particles in the blood came from the arterial wall, such as directly released from ruptured or permeable plaques. It was also possible that oxidation-specific epitopes generated in the arterial intima, such as oxidized phospholipids, might have been transported by some mechanisms to Lp(a) acceptors, or might move between LDL and Lp(a).

Elevated Lp(a) level may also result in increased circulating ox-Lp(a). Ox-Lp(a) is found related with Lp(a), which shows that more Lp(a) in subjects with high Lp(a) has chance to be oxidized *in vivo*, resulting in strong immune response and leading to the formation of Lp(a)-IC [36, 47]. In addition, Lp(a) is known to act as an acute-phase reactant in patients with ACS. It has also been found increased Lp(a) and ox-Lp(a) levels are positively related with C-reactive protein in patients with rheumatoid arthritis [47], which suggests that inflammation promotes Lp(a) synthesis and its oxidation.

One of important problems remaining to be answered is whether the response to oxidized lipoprotein plays an initiating or a contributing role in the development of atherosclerosis. To answer this question through clinical studies, one major problem is the difficulty encountered in defining atherosclerosis-free individuals. The results that high levels of anti-ox-LDL antibodies and LDL-IC are present in individuals with confirmed atherosclerosis suggest that the immune response to ox-LDL may be a secondary phenomenon, possible contributing to the development of atherosclerosis. However, the studies have shown that ox-Lp(a) and Lp(a)-IC are present in all the healthy children and especially in newborns, and that anti-ox-LDL antibodies and LDL-IC are easily detectable in asymptomatic young adults and children [45, 46, 58], for early arterial lesions may not present in all the children, which suggest that the immune response to modified lipoproteins could appear very early in the process, perhaps being one of the initiating factors. In fact, oxidative stress has been reported to be present early in pregnancy and children, and to be associated with arterial dysfunction and enhanced intima-media thickness [43, 44]. In general, it has been accepted that lipoprotein traverses the subendothelial space where it becomes oxidized, and may induce endothelial dysfunction, one of the earliest manifestations of atherosclerosis. *In vitro* and *in vivo* studies have shown that ox-LDL promotes endothelial cell toxicity and vasoconstriction [59]. The above studies suggest that part of lipoproteins have been oxidized before they traverse the subendothelial space, prior to advanced lesion formation, and directly participating in the development of atherosclerosis.

9. Lp(a) immune complexes and β_2-glycoprotein I complexes with Lp(a)

It has been proposed that modified lipoproteins might contribute to atherogenesis by another mechanism-their ability to trigger an immune response leading to the production of autoantibodies and subsequently to the formation of IC. Some studies have shown that incubation of human monocyte-derived macrophages with insoluble or soluble LDL-IC induces foam cell formation *in vitro* more efficiently than any other known mechanism [60-62]. The pathogenic role of LDL-IC *in vivo* is also supported, and the studies have shown that plasma LDL-IC level increases in patients with CAD [63, 19] and that the cholesterol content of LDL-IC is a powerful discriminator for the presence of coronary atherosclerosis [20].

Lp(a) might also trigger an immune response leading to the production of autoantibodies and subsequently to the formation of IC. Interestingly, it has been found that Lp(a)-IC was present in both the plasma of patients with CAD and control, and Lp(a)-IC level increased in the CAD patients [64]. Furthermore, Wang et al. [65] studied the plasma Lp(a) and Lp(a)-IC levels in 232 subjects with various dyslipidemias. This study showed that both Lp(a) and Lp(a)-IC levels were different in various types of primary hyperlipidemia. Moreover, it was found that plasma Lp(a)-IC levels represented the similar distribution to

that of Lp(a). In fact, both antibodies against oxidized apo(a) and apoB *in vivo* can form immune complexes with oxidative apo(a) or apoB of Lp(a). In addition, not a parallel increment between Lp(a)-IC and LDL-IC levels was found according to Lp(a) cutoff level (especially Lp(a)<300mg/l), which suggested that Lp(a)-IC level might act as an additional predictor of premature CAD [64]. Recently, Wang et al. have also found that incubation of human monocyte-derived macrophages with Lp(a)-IC induces foam cell formation by Fc γ receptor pathway *in vitro*.

It was reported that β_2-GPI was present in the sera of autoimmune diseases and was characterized by its ability to bind to negative charged molecules, including lipoproteins [66-69]. Recently, studies showed that β_2-GPI specifically interacted with LDL as well as ox-LDL, and formed complexes in the intima of atherosclerotic lesions, and then, these complexes were taken up by macrophages via anti-β_2-GPI autoantibody-mediated phagocytosis, contributing to the development of atherosclerosis [70]. *In vitro* studies also demonstrated that β_2-GPI bound Lp(a) with high affinity [71, 72], suggesting that β_2-GPI might bind Lp(a) to form complexes of β_2-GPI with Lp(a) [β_2-GPI-Lp(a)] *in vivo*. Furthermore, preliminary data suggest that additional ox-PL are present in the lipid phase of Lp(a) (Figure 5) [73].

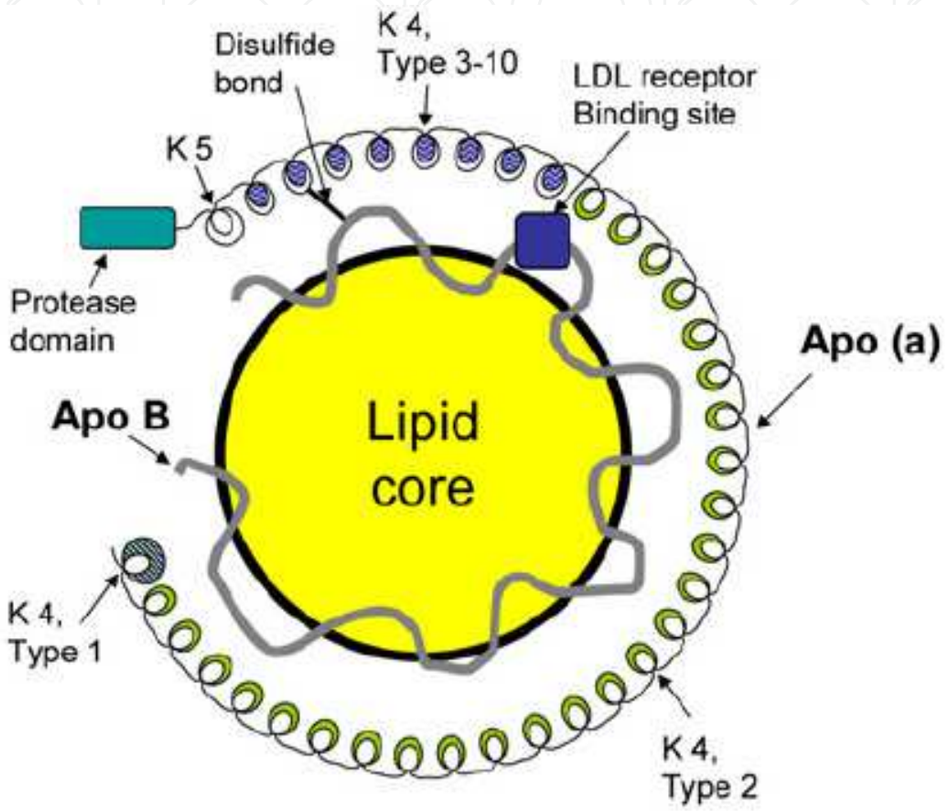
Our studies have found that β_2-GPI-Lp(a) indeed existed in serum samples, and that β_2-GPI-Lp(a) as well as ox-Lp(a) concentrations were significantly elevated in systemic lupus erythematosus (SLE) patients with excessive cardiovascular events [74], and in active rheumatoid arthritis (RA) patients [75]. Furthermore, β_2-GPI-Lp(a) levels were found increased in both the patients with ACS and stable CAD. The logistic regression analysis of risk factors revealed that the presence of β_2-GPI-Lp(a) as well as ox-Lp(a) or Lp(a) was a strong risk factor for stable CAD, and especially for ACS, suggesting that the β_2-GPI-Lp(a) complexes might act as an additional predictor of atherosclerosis [76].

An important role in the accumulation of ox-PL on Lp(a) may also be played by β_2-GPI, which binds to the kringle IV domain of apo(a) [71], as well as to anionic phospholipids and ox-PL [77]. Importantly, high β_2-GPI levels were also found on the Lp(a) of CAD patients, whereas removal of apo(a) from the Lp(a) particles of these patients led to reduction of the β_2-GPI levels and to increase in the lipoprotein-associated phospholipase A_2 (Lp-PLA_2) catalytic efficiency. Substrates for Lp-PLA_2 contain oxidatively fragmented residues at the *sn-2* position (ox-PL). Thus, the higher amounts of β_2-GPI on the Lp(a) of CAD patients could contribute to the sequestration of ox-PL on the surface of Lp(a) [78].

10. Conclusions

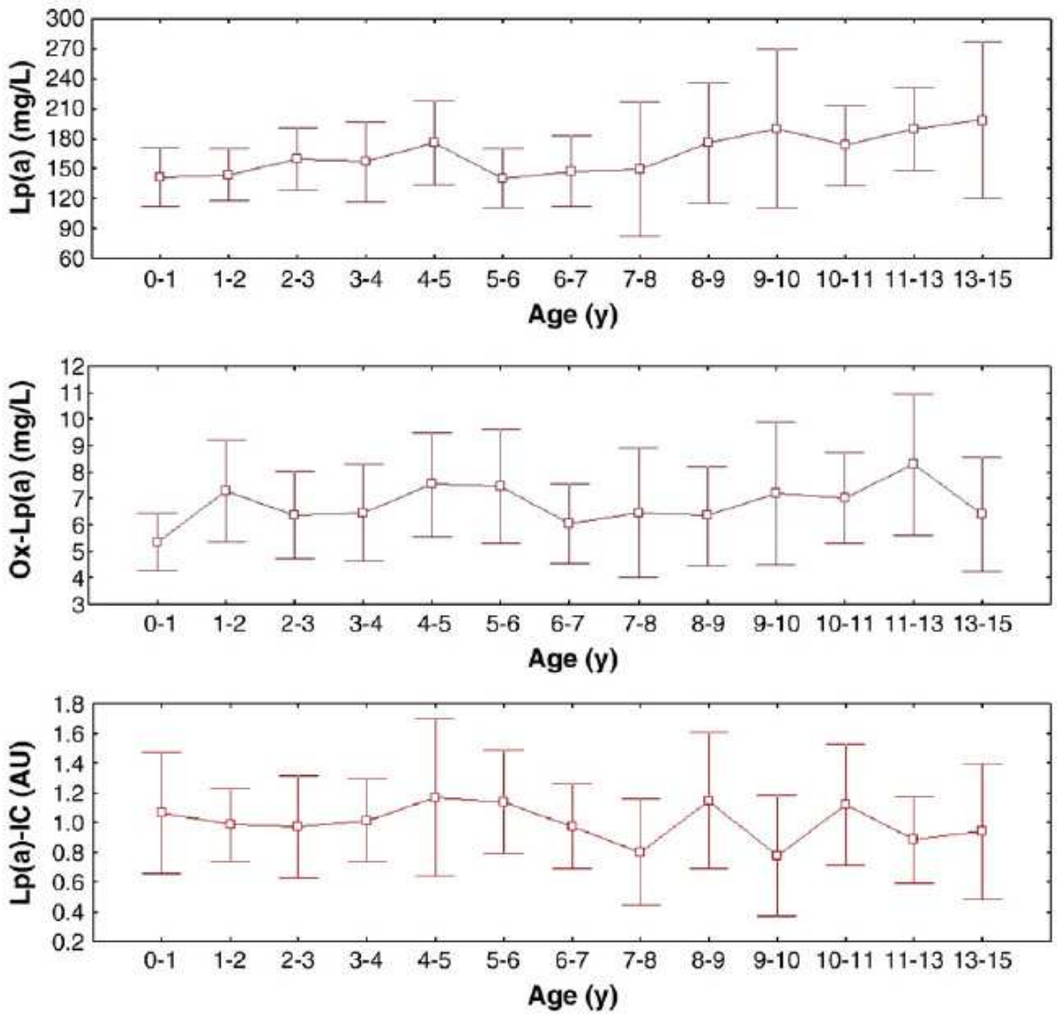
In summary, Lp(a) might be oxidatively modified *in vivo*, which causes marked changes in the structure and biological properties of Lp(a). Oxidatively modified Lp(a) has more pathogenicity in both formation of foam cells and fibrinolysis. Elevated plasma concentrations of ox-Lp(a) reflect the presence and extent of angiographically documented CAD, especially clinically expressed in ACS. The elevated plasma concentrations of ox-Lp(a) suggest plaque instability and may be useful for the identification of patients with ACS. The assay of ox-Lp(a) may provide a new approach to investigate the causal role of ox-Lp(a) in atherosclerotic cardiovascular disease in a prospective study and to explore the exact pathogenic role of ox-Lp(a).

11. Annex



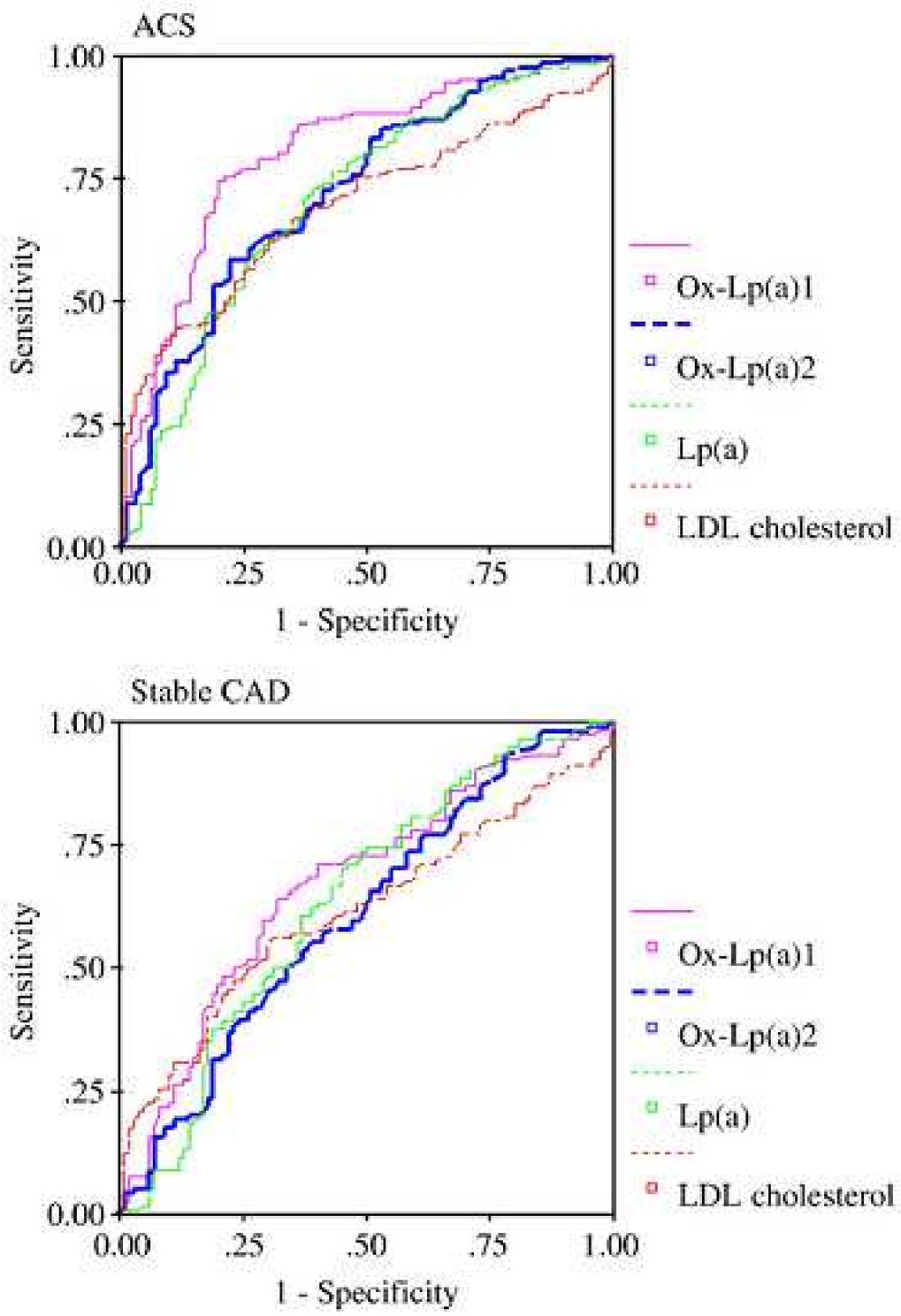
Lp(a) is an LDL-like particle composed of a lipid core (cholesteryl esters; triglycerides) encapsulated by a surface layer (phospholipid; free cholesterol). As with LDL, Lp(a) contains one molecule of apoB, linked to the apo(a) by a single disulfide bond. The apo(a) moiety consists of a single copy of kringles (K) 4, types 1 and 3 through 10, kringle 5, and a protease domain analogous to the structure of plasminogen. Lp(a) always has multiple copies of kringle 4, type 2 contributing to the abundant heterogeneity of the molecule.

Fig. 1. Schematic Model of Lp(a) Structure.



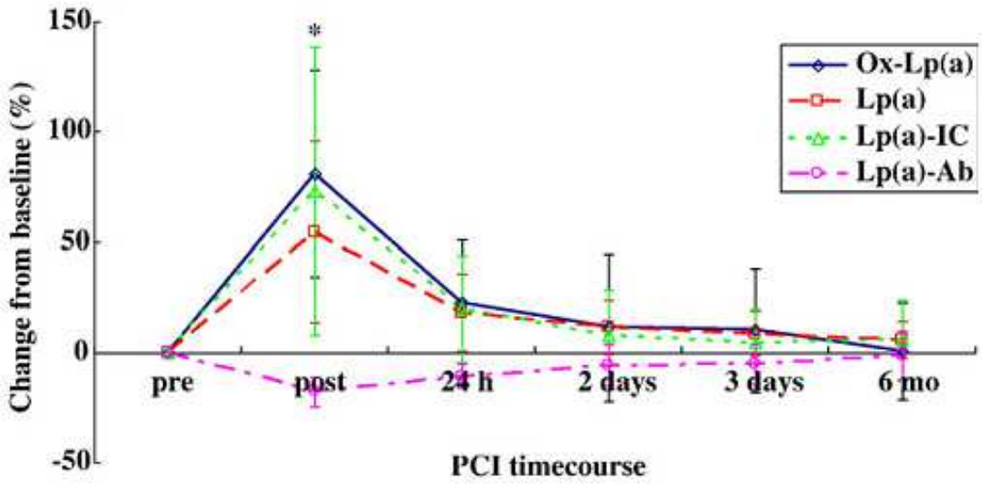
No difference of their levels was found among the age groups.

Fig. 2. Mean levels of Lp(a), ox-Lp(a) and Lp(a)-IC in each of the 13 year groups in the 747 children.



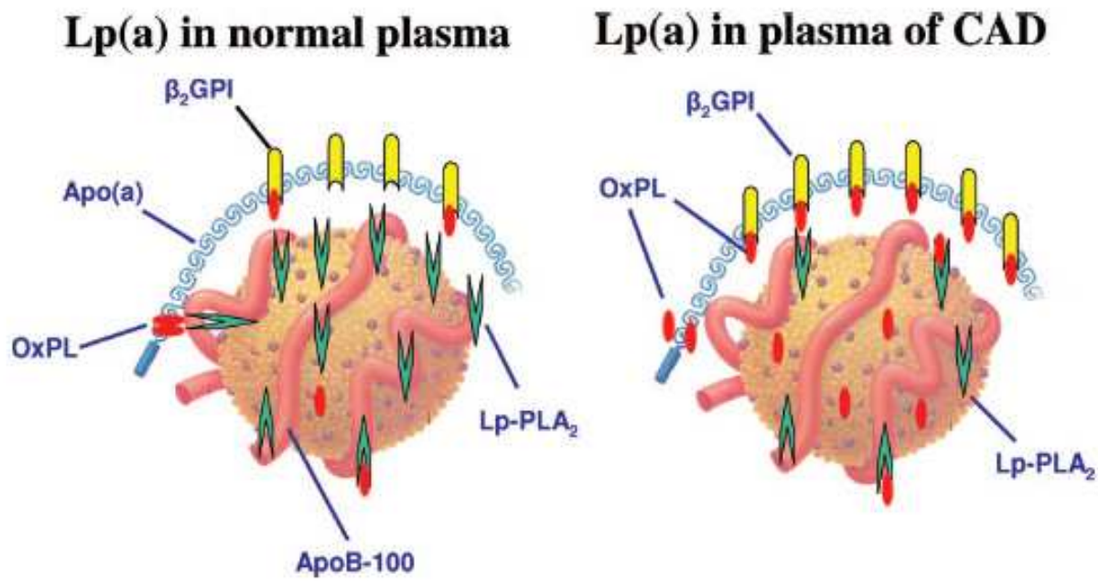
Ox-Lp(a)1: detected by anti-ox-Lp(a); ox-Lp(a)2: detected by anti-ox-LDL.

Fig. 3. Receiver-operating characteristic curve analysis of ox-Lp(a) and Lp(a) levels in patients with ACS and stable CAD.



The change is expressed as mean percent change from pre-PCI levels. * P<0.001 by ANOVA. Lp(a): P<0.001 compared with before and 6-month time points; P<0.05 compared with 2- and 3-day time points. Ox-Lp(a): P<0.001 compared with before, 3-day, and 6-month time point; P<0.01 compared with 2-day time point. Lp(a)-IC: P<0.05 compared with before, 3-day, and 6-month time point. Ox-Lp(a)-Ab: P<0.001 compared with before and 6-month time points; P<0.01 compared with 2- and 3-day time points.

Fig. 4. Changes of Lp(a), ox-Lp(a), Lp(a)-IC, and ox-Lp(a)-Ab levels after PCI.



Lp(a) of CAD patients contains higher levels of β2-GPI and ox-PL and significantly less amount of Lp-PLA2 mass compared with Lp(a) from normal plasma.

Fig. 5. Association of Lp-PLA_2 and ox-PL with Lp(a) in normal plasma as well as in plasma of patients with CAD.

12. References

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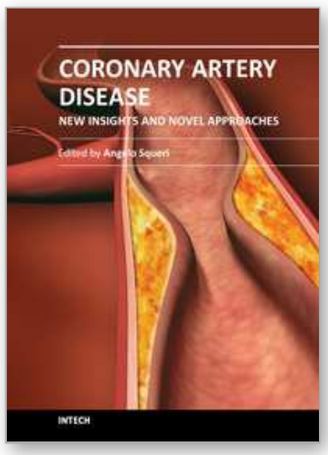

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Coronary Artery disease is one of the leading causes of death in industrialized countries and is responsible for one out of every six deaths in the United States. Remarkably, coronary artery disease is also largely preventable. The biggest challenge in the next years is to reduce the incidence of coronary artery disease worldwide. A complete knowledge of the mechanisms responsible for the development of ischaemic heart disease is an essential prerequisite to a better management of this pathology improving prevention and therapy. This book has been written with the intention of providing new concepts about coronary artery disease pathogenesis that may link various aspects of the disease, going beyond the traditional risk factors.

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