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REVIEW ARTICLE

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Analyze the Mechanistic Role of LOX-1 in Cardiovascular Diseases: A Review

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Abstract

Cardiovascular disease (CVD) is a major global health concern that leads to illness and death. One of the primary risk factors for CVD is dyslipidemia, which can cause an elevation of oxidized LDL. Recently, the lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1 receptor), a transmembrane protein found in endothelial cells, platelets, cardiomyocytes, and other cells, has gained attention. LOX- 1 receptors are responsible for recognizing oxLDL, and overactivation can trigger pathways that cause tissue damage, including endothelial dysfunction and apoptosis, process under investigation involves the following: promotion of platelet activation and adhesion to endothelial cells; ADP-mediated aggregation; and the development of cardiac fibrosis and myocyte apoptosis. Measuring soluble Lox1 (sLox1) levels in the serum may be considered a potential CVD biomarker in all stages of CVD. Synthetic Lox1 inhibitors and neutralizing antibodies have recently been developed, making Lox1 a target for drug development. This review examines the main findings of LOX1's role in development, diagnostic and treatment strategies to prevent and manage heart disease. It emphasizes the contribution from LOX1 in the pathophysiology of atherosclerosis, endothelial dysfunction and inflammation, which is important factor in the progression of CVDs. In addition, the capacity of LOX1 is discussed in the reviews, which is a biomarker for initial identity and promises it as a therapeutic goal in the innovative treatment method aimed at reducing cardiovascular risk. The conclusion of the review is as such: that LOX-1 should be considered a primary marker of CVSs, and that its inhibition should be a priority in order to reduce the risk of cardiac events.

Keywords: Cardiovascular disease, LOX-1, Oxidized LDL, Endothelial cells

1. Introduction

Lox-1, which was discovered in 1997, is a 50 kDa membrane scavenger receptor. Lox-1 is a 50 kDa type II transmembrane protein consisting of 273 amino acids [1]. It occurs as a homodimer, with a cytoplasmic short N-terminal region connected to a single hydrophobic transmembrane domain. The extracellular region includes an 80-residue coiled coil domain (NECK) coupled to the CTLD (C-terminal lectin-like domain [2].

It plays a role in internalization of LDL oxidized by different cell types, including endothelial cells, macrophages, platelets, cardiomyocytes and smooth muscle cells. The features have been seen in procedures such as OxLDL -Internalization, Endothelial Dysfunction, Atherosclerosis, Plaque instability, Thrombogenic and Congenital Immune Response [3]. Effects are disseminated by activation of intracellular routes such as nuclear factor κB, MAPK and caspases. When the outer domain of the LOX-1 is removed, the SLOX-1 is issued in circulation, and the levels

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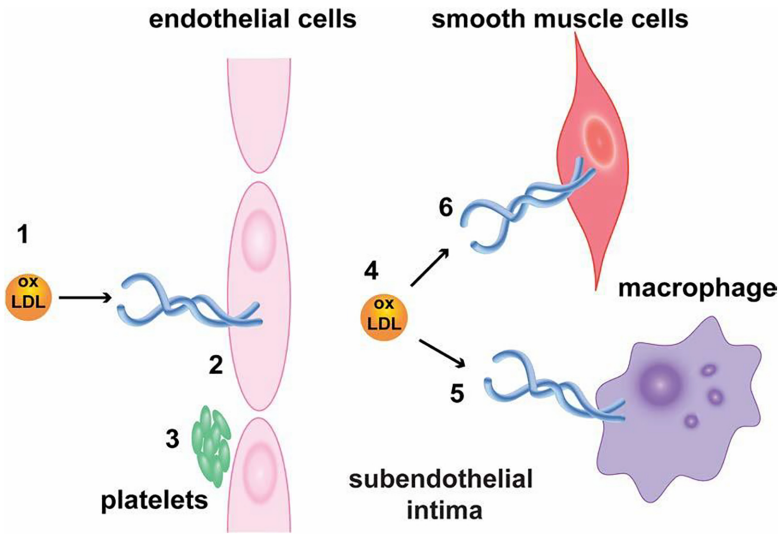

Fig. 1. The Lox-1 expression in different types of cells and its activation by oxLDL [8].

of the plasma are considered to represent the active cell-bound LOX-1. It creates a valuable biomarker to increase the evaluation of heart risk to sLOX-1 and to an initial detection of thromboembolic incidents [4].

In endothelial cells, the activation of the LOX-1 shows to increase the formation of membrane investments, which helps to lift OxLDL. It is taken to seal vesicles through the cytosol for liberation in the subendothelial team. In addition, OXLDL/LOX-1 is displayed to increase the expression of adhesion molecules, and the atherosclerotic plaque promotes recruitment of leukocytes. In addition, the LOX-1 plays a role in activating B-galactosidase and CH2AX, which is added to the rapid time for early aging of endothelial cells and endothelial dysfunction [5].

In addition, the activity of the LOX-1 adherence to the booklet of platelets in the endothelium increases, promoting the release of growth factors of platelets that help promote atherosclerotic plaques. In addition, the LOX-1 platelet activation and mediated aggregation of ADP increase, which is necessary for the formation and stability of thrombi [6]. Within the structure of macrophages, it has been shown that the LOX-1 expression increases strongly in contact with inflammatory signals. It has been shown that the construction of lipids and as a result of foam cells inside the macrophages depends a lot on this increase in expression. In addition, LOX-1 macrophage changes calcium metabolism, which helps them gather in atherosclerotic lesions. Finally, the LOX-1 manifestation is found in smooth muscle cells, where it is shown to activate the proapoptotic passage and stimulate metalloproteinases, then dilute the fibrous hat and increase the vulnerability of atherosclerotic plaque [7] (Fig. 1).

The primary objective of the present review was to evaluate the role of LOX-1 as a primary marker of cardiovascular disease (CVD) and to assess the efficacy of inhibiting these receptors in reducing the risk of cardiac events.

1.1. Lox1 structure

Lox-1 possesses the NECK domain, which was initially identified as an 80-residue α-helical coiled coil structure located near the transmembrane domain. It is linked to the CTLD through an interchain disulfide bond. When proteases cut the proximal part of the NECK domain, it releases its 34 kDa soluble forms (sLox-1) into the blood stream [1, 9]. This part of the domain is not as structurally stable as the rest of it. The cleavage of the NECK domain and the release of sLox-1 are partially mediated by IL-18 in a manner dependent on ADAM10. Additionally, the stability of the C-terminal NECK domain depends on the integrity of the CTLD, with mutations in the C140 residue impacting the NECK structure. Importantly, the NECK domain does not affect oxLDL binding affinity, as its deletion does not influence ligand-binding activity [10]. To sum up, the NECK domain is made up of an N-terminal segment close to the beginning that releases sLox-1 and a segment farther away that works with the CTLD to make it more stable. Lox-1, a membrane scavenger receptor, plays a role in the internalization of oxLDL by various cell types, such as endothelial cells, macrophages, platelets, cardiomyocytes, and smooth muscle cells. It is also associated with endothelial dysfunction, atherosclerosis, plaque instability, thrombogenesis, and innate immune responses [11].

1.2. Lox1 gene

Lox-1 is the product of the ORL1 gene, which is a single-copy gene (oxidized low-density lipoprotein lectin-like receptor 1; OMIM No. 602601) located in a C-type lectin gene. Specifically, ORL1 undergoes alternative splicing to produce 3LOX- mRNA variants: transcript variant 1 (NM002543), transcript variant 2 (NM001172632), and transcript variant 3 (NM001172633) [12]. Transcript variant 1 contains all 6 exons and results in the production of full-length Lox-1 with complete oxLDL-binding activity. In contrast, transcript variant 3 lacks exon 5, resulting in an interrupted CTLD-containing protein known as loxin. As mentioned earlier, the integrity of CTLD is necessary for ligand-binding; therefore, loxin is unable to bind oxLDL [13]. Additionally, it has been observed that loxin forms dimers with full-length Lox-1, inhibiting its ligand-binding activity. This dominant negative action of loxin suppresses oxLDL/Lox-1 signaling, oxLDL- induced positive feedback on Lox-1 expression, and subsequent proatherogenic processes. For instance, transfection of human endothelial cells with constructs overexpressing loxin led to decreased oxLDL-induced apoptosis. Furthermore, the loxin allele is relatively common in the population (20%–30%), and several studies have indicated that the presence of this allele is linked to a reduced risk of cardiovascular disease [14]. These findings suggest that promoting alternative splicing favoring loxin over Lox-1 expression could be protective. While this is a promising hypothesis, it has not been confirmed by large, randomized clinical trials. How- ever, recent observational studies have reinforced the association of SNPs with atherosclerotic cardiovascular disease [14]. The frequency of risk SNPs is higher among atherosclerotic cerebral infarction subjects compared to healthy controls in a Chinese population. Similarly, Tatsuguchi et al. found a significantly higher chance of presenting risk SNPs among individuals with myocardial infarction compared to healthy controls [15]. Predazzi et al. also found that the occurrence of a specific risk SNP (rs11053646) is associated with increased carotid intima-media thickness in a large cohort of asymptomatic male individuals, suggesting a role of this polymorphism in the initial events of atherosclerotic cardiovascular disease. Lastly, Xu et al. discovered an association between the expression of risk SNPs and the progression of left ventricle hypertrophy in hypertensive subjects [16].

1.3. LOX 1 signaling

When the Lox-1 receptor binds to a ligand, it triggers signaling that causes changes in the behavior of various cell types. These changes include reducing eNOS activity, activating NADPH, and producing reactive oxygen species, leading to increased oxidative stress and decreased availability of NO [17]. Lox-1 activation also stimulates inflammatory pathways, resulting in an increase in IL-1β production and an inflammatory response. Additionally, Lox-1 activation initiates other signaling pathways such as MAPK, protein kinase C, octamer-binding protein- 1, and PI3K/Akt, all of which alter cellular activity in the cardiovascular system and may contribute to disease progression [18] (Fig. 2).

Because LOX-1 expression in endothelial cells is usually modest in vitro, mechanical stimuli including oxidized low-density lipoprotein (OX-LDL), angiotensin II (Ang II), tumors necrosis factor-α (TNF-α) can rapidly raise its expression. Additionally noted to induce LOX-1 expression are oxidant species. Areas with atherosclerosis and other forms of vascular disease commonly feature these elements [20]. Angiotensin II, C-reactive protein, endothelin-1, glucose, histamine, homocysteine, human cytomegalovirus, interferon-γ, interleukin-1β, oxidized-low density lipoprotein, phorbol ester, shear stress, transforming growth factor-β, and tumor necrosis factor-α are among the stimuli that cause LOX-1 to be upregulated. Increased LOX-1 levels can result from a number of conditions, including atherosclerosis, diabetes, high blood pressure, high cholesterol, tissue injury from inadequate blood flow, and organ transplants [19].

1.4. Measurement of serum sLox1 as a biomarker of CVD

A growing body of evidence supports the role of Lox-1 in the progression of atherosclerosis and its potential negative impact on clinical recovery from ischemic events. While direct measurement of cellular Lox-1 levels is not possible, validated assays for soluble Lox-1 (sLox- 1) are available and used to assess its utility in cardiovascular risk estimation for guiding preventive medical strategies. For example, a recent study with 2437 participants over 11 years found that those in the highest quartile of sLox-1 had increased risks of stroke and coronary heart disease compared to the lowest quartile [21]. sLox-1 has also been explored as a potential biomarker for early identification of acute coronary syndrome (ACS).

In a study compared to SLOX-1 with traditional biomarkers such as CK-MB and troponin T in ACS patients, SLOX-1 showed high sensitivity to detect the STEMI and NSTEMI. In addition, the level of elevated SLOX-1 was associated with important acute cardiovascular phenomena in patients who underwent primary percutaneous intervention [22]. Similarly, the

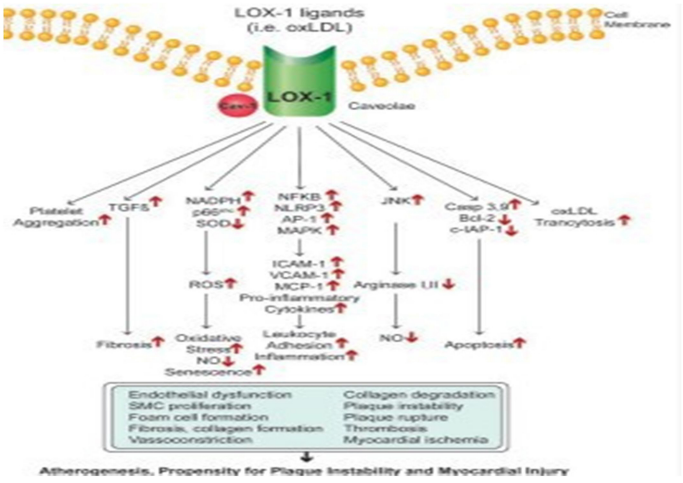

Fig. 2. Lox-1 signaling pathways [19].

level of SLOX-1 is associated with the occurrence of stroke, where high SLOX-1 levels are associated with increased stroke risk in different studies. In particular, the level of elevated SLOX-1 has been found in individuals with a history of ischemic stroke or severe carotid atherosclerotic disease. In addition, in individuals with acute ischemic stroke, elevated SLOX-1 levels were associated with poor long-term functional results and more serious blows [23]. These findings suggest a potential role for SLOX-1 as a pathological biomarker in ACS and stroke. Research mentioned that the elevated level of SLOX-1 was associated with various cardiovascular phenomena that included the most important side effects (MACE), stroke and coronary heart disease (CHD). High SLOX-1 levels were often associated with poor results, such as increasing risk of MACA in CAD patients, passed through PCI, poor improvement after ischemic stroke, and high risk of stroke and CHD in different populations [24]. In addition, individuals with complex coronary lesions and broken plaque had more SLOX-1 level than people with simple lesions or stable angina pectoris. Clinical testing and frequent inflammation that assesses the safety and efficacy of a drug (MEDI 6570) in individuals with type 2 diabetes or earlier MI showed promising results in the context of monitoring side effects and changes in plaque volume [25].

2. Pathophysiological role of LOX-1

2.1. Role in oxidative stress and inflammation

Angiotensin-converting enzyme (ACE) and Ang II type 1 (AT1) receptor expression activate the renin-angiotensin system (RAS), a potent mediator of atherosclerosis, reducing atherogenesis through RAS suppression while increasing the expression of both ACE and AT1 receptors in the developing inflammation [26].

Ang II through the Ang 1 receptor is displayed to promote the synthesis of LOX-1 in a transcript pathway and improve the absorption of OX-LDL in endothelial cells in human coronary arteries. It turns out that both OX-LDL and Ang II inspire equivalent intracellular routes, resulting in cell activation and damage. These procedures are considered to be the antecedents and myocardial ischemia. As a result, the concept is presented with a positive crosstalk between dyslipidemia and RAS [27] as seen in Fig. 3.

Numerous investigations have demonstrated that oxidant species, such as H2O2, increase the production of LOX-1 in fibroblasts, smooth muscle cells, and endothelial cells. It was recently demonstrated that oxidative stress and LOX-1 expression are linked to balloon catheter-induced rat carotid injury. M40401, a strong antioxidant, simultaneously decreased carotid injury and downregulated LOX-1 expression [28]. One of the primary regulators of LOX-1 overexpression is the peroxisome proliferator-activated receptor-α (PPAR-α). According to recent research, PPAR-γ activators can prevent TNF-α from inducing LOX-1 expression in cultured bovine aortic endothelial cells [29]. Ox-LDL and Ang II-induced oxidative stress and LOX-1 overexpression in coronary artery endothelial cells and fibroblasts can be inhibited by the PPAR-γ ligand pioglitazone, and NF-κB is a powerful factor in pioglitazone's actions. Activating protein-1 (AP-1) mediates the increase of LOX-1 brought on by glucose [30]. According to related research, several signaling pathways, such as p38 mitogen-activated protein kinase (MAPK), p44/42 MAPK, protein kinase C (PKC), protein kinase B (PKB), and protein tyrosine kinase (PTK), drive the activation of these redox-sensitive transcription factors [31] (Fig. 3).

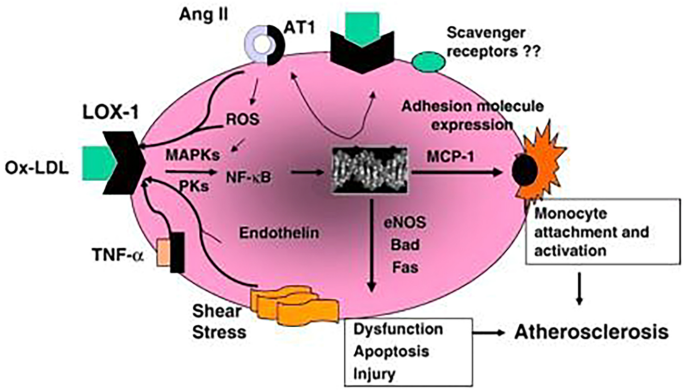

Fig. 3. Activation of both AT1 and LOX-1 receptors via redox signaling leads to cell breakdown up to in apoptosis and harm to cells, monocyte adhesion and activation and eventually atherosclerosis [32].

2.2. Role in endothelial injury

Endothelial cells play an important role in the transport of LDL particles from vascular lumen to subendothelial intimate. This process involves transcytosis, where LDL is internal, seals through cytosols in seals and is released into the subendothelial area. Caveolae, a membrane containing the cave -1 in the membrane, plays an important role in this process. LDL is transported through endothelial cells in special vesicles and transported to subendothelial rooms by exocytosis [33]. In atherosclerosis, the formation of Caveolae is important, as it contributes to the recruitment of monocytes in the endothelium layer and then contributes to the formation of proatherogenic foam cells. LOX-1 plays an important role in promoting monocytadhesion for an endothelial cell and starting atherosclerosis by facilitating the transmission of oxLDL to osteosclerosis. In addition, the LOX-1 has proven to convey the OXLDL-induced endothelial cell dysfunction and tendon, which can contribute to the progression of atherosclerosis [34]. When maintained in the subendothelial layer, OxLDL can be attached by macrophages to make cholesterol -rich foam cells. Macrophages use different mechanisms to lift LDLs, including LDLR, receptor-independent fluid-side-endocytosis, and scavenger receptors such as LOX-1 [35]. LOX-1 expression has been upgraded in response to inflammatory stimuli and hyperglycemia, causing cellular lipid accumulation and macro storage activation. LOX-1 activation also affects the production of inflammatory elevation, mitochondrial DNA damage and production of reactive oxygen species in macrophages, contributes to atherosclerotic plaque formation and progression [36].

2.3. Role in foam cell formation

After being trapped in the subendothelial layer, oxidized LDL is encased in the extracellular matrix and can be taken up by macrophages, forming foam cells that contribute to the development of atherosclerotic plaques. Macrophages in the vascular intima become cholesterol-rich foam cells through three main mechanisms: LDLR, receptor-independent fluid-phase endocytosis, and scavenger receptors like Lox-1 [37]. Despite LDLR being present on cell surfaces and responsible for internalizing LDL when cholesterol levels are low, foam cells can still form in LDLR-deficient models, suggesting that other mechanisms contribute to cholesterol storage in macrophages. Studies have shown that macrophages can engulf LDL through fluid-phase endocytosis, where they fuse with vacuoles carrying fatty material and LDL particles from the vascular intima. This process is not regulated by intracellular cholesterol levels and the uptake of LDL is directly linked to its concentration in the subendothelial [38]. Although most LDL uptake by macrophages is through the mentioned mechanisms, Lox-1 only accounts for a small percentage of oxidized LDL uptake. Lox-1 is minimally expressed in resting macrophages but becomes significantly upregulated under inflammatory conditions and hyperglycemia, leading to increased lipid accumulation and macrophage activation [39]. Activation of Lox-1 also triggers NRLP3 inflammasome activation, mitochondrial DNA damage, and the production of reactive oxygen species in active macrophages. Additionally, activated Lox-1 inhibits calpain1 and increases calcium levels, which impairs macrophage migration and contributes to their retention in atherosclerotic lesions H2O2 [10].

2.4. Role in platelets dysfunction

Coronary artery blockage caused by the formation of blood clots over ruptured plaque in the arteries is the main reason for ischemia and heart attacks [40]. Both the adhesion of platelets to the endothelium and the aggregation of platelets that lead to the

formation of occlusive blood clots are influenced by Lox-1. In addition to their role in blood clot formation, platelets also contribute to the progression of atherosclerosis by producing various growth factors that promote the growth of plaque in the arteries [41]. Platelets adhere to the endothelium, absorb, and move to the area below the endothelium where they release growth factors that promote atherosclerosis. It has recently been shown that the expression of Lox-1 by endothelial cells is involved in the adhesion of platelets to the endothelium [42]. For example, treatment of endothelial cells with LOX-1 inhibitors reduces platelet adhesion half and reduces the activation of downstream routes that contribute to endothelial dysfunction. In addition, it reduces preventing LOX-1 in Vivo tissue factor and contact with PAI-1, which facilitates the recruitment of platelets for atherosclerotic plaques, causing blood clots to form ([10, 43]). The recent discovery of LOX-1 on the surface of platelets has made an intensive discovery for its potential role in platelet collection and blood clotting. In vitro models show that LOX-1 is stored in platelet granules and presented on the surface of the cell when platelets are activated by external stimuli such as oxidized LDL, shear stress and pregnancy cytokines [44]. Because LOX-1 recognizes and binds the platelets that are active in the surrounding area, it is intended that the LOX-1 may include the platelet plate interactions, promotes aggregation and formation of stable blood clotting [45]. cultured platelets to modified LDL induced ADP-mediated platelet aggregation, an effect that was inhibited by pretreatment with Lox-1 inhibitors. Taken together, these data suggest that while Lox-1 from endothelial cells promotes platelet adhesion and the exposure of tissue factor and PAI-1, the presentation of Lox-1 by active platelets significantly enhances their ADP-mediated aggregation [46].

3. Role of LOX-1 in pathological conditions

3.1. LOX-1 correlated with hypertension

In several rat designs, LOX-1 gene expression is associated with hypertension. In the aorta of normotensive rats, LOX-1 mRNA expression is low, but it is significantly higher in spontaneously hypertensive rats and salt-loaded Dahl salt-sensitive rats, according to studies [47]. This overexpression of LOX-1 has been linked to a number of clinical disorders and is associated with hypertension. Furthermore, aldosterone/salt-induced hypertensive rats treated continuously with eplerenone, an aldosterone receptor antagonist, disrupted LOX-1-mediated pathways, indicating that LOX-1 may be involved in the kidney damage linked to hypertension. [48]. Deletion of LOX-1 reduced renal damage following Ang II infusion in Ang II-infused LOX-1 knockout and wild-type mice, indicating that LOX-1 is essential for the onset and maintenance of hypertension and the ensuing end-organ damage. Moreover, in salt-loaded Dahl salt-sensitive rats, LOX-1 is increased in kidneys linked to glomerulosclerosis. All things considered, the data point to the significance of the LOX-1 gene in the pathophysiology of hypertension by suggesting that its expression is connected with hypertension in a number of rat models [49].

LOX-1 is a receptor that binds multiple ligands including ox-LDL, hypochlorite-modified high density lipoprotein, aged red blood cells, apoptotic cells, leukocytes, bacteria, activated platelets, phosphatidylserine, and advanced glycation end products [44]. LOX-1 expression is low in normotensive rats but is upregulated in hypertensive rats, suggesting a correlation between LOX-1 and hypertension. Activation of LOX-1 by factors like Ang II can induce oxidative stress, leading to hypertension and cardiac remodeling. Inhibition of LOX-1 has been shown to attenuate hypertension, cardiac remodeling, and renal injury in animal models [50]. The LOX-1 route is considered important in the development and progress of high blood pressure and related organ damage. Further studies have shown that the LOX-1 expression can be modified by factors such as aldosterone receptor, taurine and Atorvastatin, highlighting potential therapeutic goals for hypertension-related complications [51].

3.2. LOX-1 is involved in renal injury and end-organ damage

The LOX-1 plays an important role in the injury to the end force when it comes to kidney damage and high blood pressure. Studies have shown that the manifestation of the height of the LOX-1 in the kidney is associated with conditions such as glomerulosclerosis in mice with high blood pressure [52]. In addition, chronic administration of medicines as an aldosterone receptor antagonist to mice with high blood pressure LOX-1 mediation molecules and squares, improves endothelial functions and Reno potions. The protective effects of substances such as Torin or atorvastatin in hypertension-induced kidney damage are also associated with oppression of LOX-1 suppression [53]. In Ang II-infused hypertensive mice, deletion of LOX-1 was found to attenuate renal injury, with less glomerulosclerosis, arteriolar sclerosis, tubulointerstitial damage, and renal collagen accumulation compared to wild-type mice. Reduction in collagen formation and improvements in endothelial

nitric oxide synthase expression were observed in the kidneys of LOX-1 knockout mice, indicating a pivotal role of LOX-1 in the onset and sustenance of hypertension and end-organ damage [54]. Overall, LOX-1 exacerbates renal injury and end-organ damage in the context of hypertension through various mechanisms related to oxidative stress, vascular lipid retention, and signaling pathways activation [55]. Its interaction with factors like Ang II, oxidative stress, and ROS generation contributes to the progression of hypertension and associated complications in different organs, including the kidneys. Therefore, targeting LOX-1 could be a potential therapeutic strategy for mitigating renal damage and end-organ complications in hypertension [56]

3.3. The effects of LOX1 in myocardial ischemia and fibrosis

Expression of Lox-1 has been linked to the inflammatory response and cardiac remodeling after an ischemic injury. During myocardial ischemia, Lox-1 expression is increased, leading to cardiomyocyte apoptosis, inflammation, and fibroblast activation, ultimately causing myocardial fibrosis and loss of function [57]. These effects are partially regulated by the MAPK and TGF-β1 pathways, making them potential targets for managing myocardial infarction (MI) and heart failure (HF) [58]. In mice with chronic ischemia induced by left coronary artery occlusion, Lox-1 expression was doubled. However, Lox-1 knockout (KO) mice did not show this increased expression and exhibited improved myocardial recovery, including increased ejection fraction and reduced infarct size compared to wild-type mice [11, 30]. The LOX-1 activation led cardiomyocyte apoptosis, conveyed by the MAPK route, which was converted by the LOX-1 ban. In addition, the LOX-1 ban in ischemia-refusal injured apoptosis and inflammation, resulting in a small infarction size [59]. The role of LOX-1 in myocardial fibrosis has also been investigated. Studies have shown that OXLDL induces cardiac fibroblast discrimination in myofibroblast, increases collagen secretion and promotes cardiac fibrosis [60]. These effects were stopped in LOX-1-KO mice. In the doxorubicin-inspired cardiomyopathic model, the LOX-1-KO mice reduced the level of LOX-1, TNFA and IL-1β compared to wild mice, causing low fibrosis and low myocardial infiltration to reduce [11]. Echocardiography also showed preserved cardiac function in Lox-1-KO mice following doxorubicin injection. Overall, these findings suggest that Lox-1 activation by oxLDL contributes to fibrosis and cardiac dysfunction after ischemic injury or cardiomyopathy, highlighting the potential of Lox-1 inhibitors as cardioprotective treatments for these conditions [61].

3.4. The effects of LOX1 in diabetes mellitus

Oxidative stress, endothelial dysfunction, and elevated adhesion molecule expression in inflammatory cells are the hallmarks of diabetes. According to an in vitro investigation, glucose increases the expression of LOX-1 in endothelial cells and macrophages [62]. In comparison to rats without diabetes, Kita et al. discovered that the aortas of diabetic rats had higher levels of LOX-1 expression. Therefore, it is not unexpected that atherosclerosis is more likely to occur in diabetics. Remarkably, LOX-1 is essential for controlling adipocyte lipid metabolism and potentially insulin sensitivity through PPARγ ligands [3, 63].

3.5. The effects of LOX1 in inflammation and immune response

One of the first stages of bacterial infection has been thought to include bacterial adherence to vascular endothelial cells, as well as mucosal and epithelial cells [64]. There may be a role for LOX-1 in the process of bacterial inflammation because of its previously reported ability to promote the adherence of both Gram-positive and Gram-negative bacteria to vascular endothelial cells [65]. It has also been shown that LOX-1 plays a role in leukocyte recruitment and infiltration in vivo as well as endotoxin-induced inflammation. According to a recent study, LOX-1 plays a crucial role in the activation of dendritic cells and macrophages in the setting of pneumonia [66]. Moreover, elevated LOX-1 mRNA expression has been noted in brain lesions in vivo as well as in S. aureus-stimulated glia in vitro [67]. Inflammatory cytokines like TNF-α and transforming growth factor-β (TGF-β) upregulate LOX-1. Furthermore, in vivo research has demonstrated a spatial relationship between LOX-1 expression and the location of these cytokines in advanced atherosclerotic lesions. Thus, these findings suggest that LOX-1 contributes to inflammation and the immunological response [68].

4. LOX-1 as a potential target for clinical trials

The encouraging outcomes seen in preclinical studies with Lox-1 inhibitors have generated significant interest in advancing these findings to clinical settings. There are currently two clinical trials in progress [69]. LOX-1, a key player in numerous pathways involved in atherosclerosis and associated conditions, is identified as a promising target for therapy. Existing treatments like aspirin, pravastatin,

and oral hypoglycemic agents impact the expression of LOX-1 indirectly ([10, 70]). Moreover, several naturally-occurring compounds and commonly used herbal medications have been discovered to alter LOX-1 expression and influence different stages of atherosclerosis [71].

It is shown that there are a specific plants and plant extracts reduce the expression of a certain protein associated with atherosclerosis. Oxidized low-density lipoprotein (OX-LDL), produced ROS brought by Berberine can help prevent atherosclerosis by reducing the generation of ROS brought by Berberine [72]. Another natural occurrence with antioxidant properties that can prevent the activation of protein known as STAT3 is Quercetin. This in turn can prevent the synthesis of fat in macrophages, which are cells that are stuck in the process of atherosclerosis, and the expression of a protein known as LOX-1 [73].

Furthermore, Danshen, a medicinal herb used to treat a number of cardiovascular diseases, contains dihydrotanshinone I [74], which has been shown to lower oxidative stress and LPS-induced LOX-1 expression in human umbilical vein endothelial cells. In vivo studies employing ApoE mutant mice given dihydrotanshinone I have also demonstrated a decrease in LOX-1 expression, oxidative stress, and atherosclerotic plaque formation [75].

Apart from the natural compounds, RNA interference methods, structure-based drug design, and the use of monoclonal antibodies are being used to create synthetic LOX-1 modulators. These modulators are designed to prevent ox-LDL and LOX-1 from interacting [76]. For example, compounds such as Plazpc have been created to interfere with interactions between OX -LDL and LOX -1. In addition, the use of microRORS and little intervention RNA for banning LOX-1 production and OX-LDL recording has been investigated in many cell types ([13, 71]). In addition, the study has shown that LOX-1 is involved in a collagen statement, leading to scarring and rebuilding in the ischemic heart. Furthermore, the study has indicated that the heart model signal was reduced as a result of the LOX-1-gene lighting, resulting in persistent heart shrinkage during myocardial ischemia [61, 77].

Overall, different approaches that are targeted against LOX-1 promising roads for atherosclerosis and potential therapeutic intervention in related diseases provide. The capacity of LOX-1 as a medical target has been indicated by its function in many passenger of ethnerogenesis and related diseases. A significant selection of modern medicines, including aspirin, statin and oral hypoglycemic medications, has been reported to show indirect effects on LOX-1 manifestation [78]. A number of naturally occurring compounds and often used herbal medicines have been shown to modify the LOX-1 manifestation, affecting different stages of atherosclerosis. Ginko biloba extracts, curcumin, negotiating cream and alasinic acid have been shown to reduce the expression of LOX-1 [79]. Resveratrol, Tanshinone II-A and Berberine have been shown to reduce the OX-LL-induced ROS generation, so help the elimination of atherosclerosis [12, 80, 81]. Quercetin, an antioxidant, has been shown to inactivate the STAT3 signaling pathway, thereby reducing ox-LDL- and LPS-induced LOX-1 production and lipid accumulation in macrophages [82].

Dihydrotanshinone I, the active component of danshen, a medicinal plant used for various cardiovascular ailments, has been shown to reduce LPS-induced LOX-1 expression and oxidative stress in human umbilical vein endothelial cells [83]. In vivo investigation utilizing ApoE mutant mice fed with dihydrotanshinone I also demonstrated a reduction in the LOX-1 expression, oxidative stress and atherosclerotic plaque formation [84]. In a recent study, traditional Chinese medicine, effectively reduced the expression of LOX-1 and the concentrations of cholesterol, LDL-C, and triglycerides in apolipoprotein E gene knockout mice [85].

The production of synthetic LOX-1 modulators is currently underway, with research focusing on RNA interference techniques, structure-based drug design and the use of monoclonal antibodies [86]. The structural structure of LOX-1 comprises a hydrophobic tunnel, which functions as the primary binding site for the phospholipid moiety of ox-LDL [87]. The binding of molecules in this tunnel has been shown to inhibit the interaction of ox-LDL and LOX-1, and the research of such molecules is currently underway. One such chemical, created by Falconi et al., PLAzPC, has been demonstrated to dramatically reduce the interaction between ox-LDL and LOX-1 [88].

By applying virtual screening approaches, molecular structure databases have been thoroughly investigated, resulting to the identification of five compounds by Thakkar et al. that hold the potential to inhibit LOX-1 [89]. Of these, two medicines have been discovered to drastically reduce downstream signaling, LOX-1 mRNA expression and ox-LDL absorption in endothelial cells. MiRNAs are noncoding RNAs that modify the gene expression by exerting post-transcription effects [90]. The Let7g microRNA has been employed to lower LOX-1 expression and ox-LDL absorption in human aortic smooth muscle cells [91]. The use of short interfering RNAs, such as antisense OLR1, has been found to result in the downregulation of LOX-1 mRNA and protein synthesis by the RNA interference approach. However, the creation of monoclonal antibodies against LOX-1 presents substantial problems, principally due to the highly conserved C-type lectin domain of LOX-1 seen across various mammalian species [92].

However, research using chimeric chicken-human antibodies has showed the capacity to disrupt the LOX-1 functions and lower the ox-LDL absorption [93]. These antibodies were created by immunizing chickens with a recombinant human LOX-1. Further efforts are underway to create these chimeric drugs for therapeutic use [12, 94]. LOX-1 has also been involved in collagen deposition leading to scar formation and remodeling in the ischemic heart. LOX-1 gene deletion has been demonstrated to attenuate cardiac remodeling signals, resulting in a preserved cardiac contractility following a persistent myocardial ischemia [95].

5. Conclusion

Over the past years, Lox1 has emerged as an attractive target for prediction, diagnosis, and treatment of CVD. It participates in all primary phases of atherosclerosis and supports the advancement of atherosclerotic CVD.

Ethical issue

Research Ethics Committee has confirmed that no ethical approval is required.

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List of abbreviations

CVD:	Cardiovascular disease
LOX-1 receptor:	the lectin-like oxidized low-density lipoprotein receptor 1
ADP:	Adenosine diphosphate
sLOX-1:	soluble Lox1
CTLD:	C-terminal lectin-like domain
LDL:	Low Density Lipoprotein
OxLDL:	oxide Low Density Lipoprotein
eNOS:	Endothelial nitric oxide synthase
NADPH:	Nicotinamide adenine dinucleotide phosphate
IL-1β:	Interleukin-1 beta
Ang II:	angiotensin II
TNF-α:	tumors necrosis factor-α
STEMI:	ST Elevation Myocardial Infarction
NSTEMI:	Non-ST Elevation Myocardial Infarction
ACS:	Acute Coronary Syndrome
MACA:	Main Arterial Coronary Artery
ACE:	Angiotensin-converting enzyme
AT1R:	Ang II type 1 Receptor
NF-κB:	Nuclear factor kappa B
MAPK:	Mitogen-Activated Protein Kinase
TGF-β:	Transforming Growth Factor-B

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