JCHR (2021) 11, 71-83

Journal of Chemical Health Risks

www.jchr.org

REVIEW ARTICLE

Role of Oxidized Low-density Lipoprotein in Human Diseases: A Review

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(Received: 27 April 2021 Accepted: 30 July 2021)

KEYWORDS

Oxidized LDL;
Blood pressure;
Renal failure;
Polycystic ovary syndrome;
Fatty liver

ABSTRACT: The current study aims to know the role of low-density lipoprotein (LDL-C) on several variables, as well as its role in diagnosing some diseases by observing its metabolism processes in many diseases affecting humans and the imbalance, is significant in the level of this lipoprotein, which constitutes an essential factor of Risk factors for developing many diseases, especially cardiovascular disease. The present study aims at assessing the oxidized LDL role in pathogenesis.

INTRODUCTION

The concept that oxidative stress and low-density lipoprotein (LDL) stress might have an effect on many diseases arose over three decades ago [1].

All cells of cellular tissue must extract energy necessary for life [2], the process of oxidation is considered one of the sources of energy supply [3]. The oxidative process accompanies the emergence of oxidative stress, significantly when the oxidation process has exceeded the normal limits [4].

Several modifications that occur as a result of stimulation of free radicals of lipid oxidation occur with the effect of oxygen on LDLP. It is expressed in a genetic term called ox -LDL. This protein is responsible for many diseases and infections and has been recognized by the body's immune system [5].

Oxidative LDL (ox-LDL) is known as LDL particles with oxidative damage: original LDL particles include around 700 phospholipid molecules, 600 free cholesterol molecules, 1600 ester cholesterol molecules and 185 triglyceride molecules, and apolipoprotein B-100 (apoB-100) with 4,536 amino acids [6].

The process of accelerating and supporting the production of reactive oxygen species (ROS) is carried out by foamy macrophages [7], causing arteriosclerosis, inflammatory responses and fat accumulation [8]; thus increasing cholesterol deposits in the walls of blood vessels [9]. The relationship between oxidative stress and inflammation is described as symmetric [7].

The cells' defense capacity collapses when they are attacked by reactive oxygen species (ROS) [10] and then the so-called oxidative stress occurs. The particle that is most vulnerable to oxidation is the low-density lipoprotein [11], thus we find that the plasma is filled with OX-LDL particles. Amidst these facts, elevated plasma OX-LDL level appears as a mortality marker [12] in chronic heart failure patients, and this condition is the result of previous oxidative stress.

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DOI: 10.22034/jchr.2021.684227

The oxidization of both lipids and proteins is possible. Native LDL oxidation is a complicated process and is divided into three stages. Endogenous antioxidants like Vitamin E are used in the initial stage known as the lag phase [13]. polyunsaturated fatty acids (PUFAs) can be quickly oxidized into fragments of fatty acids in LDL's lipids during the proliferation phase [14], oxygen-free radicals, and oxidized phospholipids (ox-PL). Fatty acid fragments are transformed into aldehyde during the decomposition stage [4], interact to form new epitopes with the lysine residue of apoB-100 [15]. LDL ability for binding to the LDL-Rs on macrophages is inhibited by these new epitopes [16]. There is a chemical association between oxidative stress and elevated generation of oxidizing species [17] or a reduction in antioxidant defense efficiency [18] like decreased catalase, catalase, glutathione, peroxidases, and others. Cell death and proliferation is vital to atherosclerosis [19] and severe oxidation might lead to the death of the cell and even slight oxidation can lead to apoptosis and cell stress, whereas necrosis can be caused by increased stress [20]. ROS and other oxidative species are constantly produced by xenobiotic and normal metabolism, ionizing radiation, exposure to the smoke pulp, etc. [21]. Depending on their concentration, oxidative molecules may have a negative or positive impact on tissues and cells. In some physiological cell processes, like signals and regulatory cascades, ROS plays an important role. Nevertheless, structural and chemical changes can be caused by excesses that have been confirmed to change cellular function, hinder protein function, lead to damage to DNA, activation of virus, and lipid peroxidization that may raise the cell death (Fig. 1) [4]. Now there is clear evidence that in many diseases' LDL oxidation is an important factor. This has been shown all the time. Therefore, it is only possible to find 10,708 releases associated with keywords Oxidized LDL until the day when PubMed entry is considered.

Studies indicate that several methods have been discovered that are able to alter the structure of LDL [1]. These studies have been conducted *in vitro* and *in vivo*. Understanding the reality of these pathways explains the relationship between LDL oxidation and the diseases [22] that result from it, thus working on the possibility of reducing the oxidation process by providing antioxidants that protect our bodies from the consequences of oxidative stress [23, 110]. Determining such pathways is usually a difficult task. Yoshida and his colleagues [24] conducted a study in which he observed high lipid peroxidation of samples isolated from human arteries affected by (atherosclerosis). He also noted that there was no shortage of antioxidant vitamins such as ascorbic acid and alpha. Tocopherol and here the understanding is further complicated. In the early post-carotid endarterectomies restenosis, LDL oxidation can play an important pathogenic role. It must develop a new therapy for carotid restenosis prevention, such as the use of antioxidants or even immunosuppressive drugs during the surgery [25].

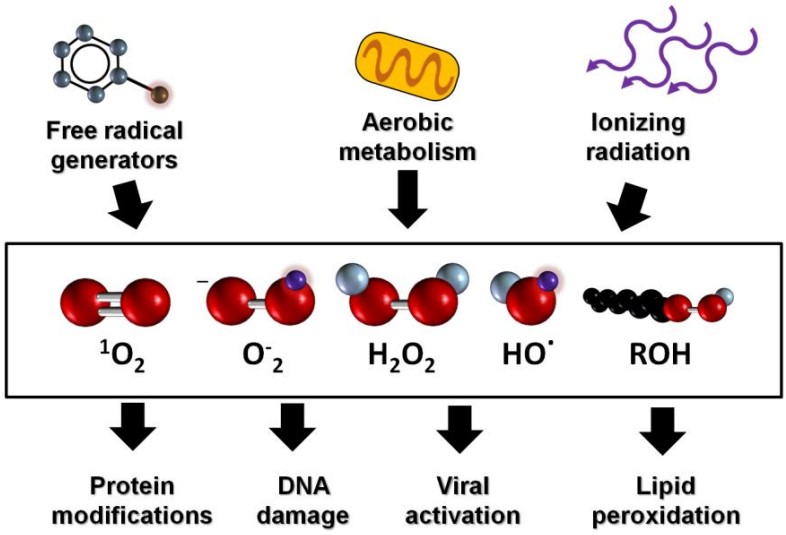

Figure 1. The sources and consequences of oxidative stress.

In vitro, LDL oxidation can occur in two stages [26]. The first stage: changing the design of lipoprotein B100 [27], called LDL, at the time, with modified LDL, as it possesses an affinity for LDL receptors [28] and maintains negative charge, also activates the anti-apoptotic signal [29], and finally stimulates inflammatory cells such as chemokines and cytokines (Figure 2); which the particles LDL and mLDL enter the subendothelial space through various paths. Macrophages and VSMCs that have acquired phagocytic phenotype can be taken up once inside the vascular wall. Much of mLDL is internalized through scavenger receptors in the cells. Foam cells in the developing atherosclerotic plaque are responsible for intracellular lipid storage [2, 26]. Stage 2: Oxidative stress continues extensively, resulting in lost recognition of the LDL receptors [30] and the conversion to OX-LDL and thus the emergence of foam macrophages. This type of LDL oxidation has effects on vascular cells [31]. Time has a slow role [32] in oxidative stress development, affecting the death of macrophages [33] in later stages of the condition, and a necrotic nucleus ruptures the plaques.

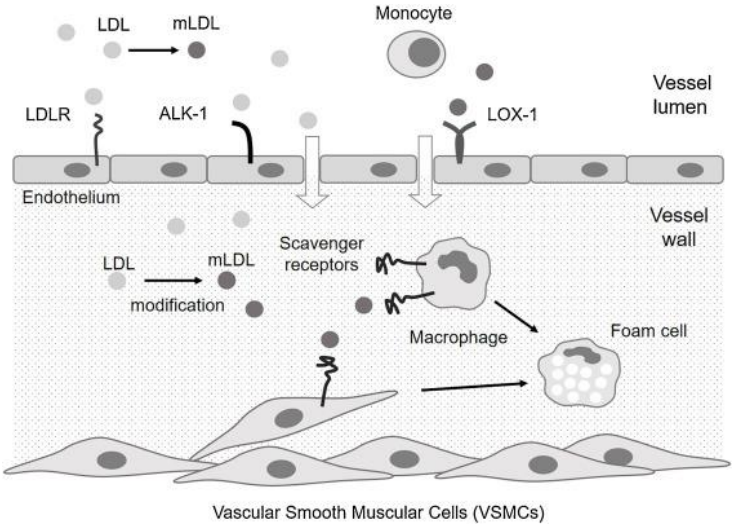

Figure 2. Simplified scheme for the formation of foam cells in the subendothelium[2].

The mechanisms of LDL oxidation In Vitro

The mechanisms are as follows:

Metal ions

There are transition minerals (specific concentrations of iron or copper) that break down the carbon and carbon bonds in the lipid peroxide compounds and lipid hydroperoxides, and form the essential aldehydes for the cholesterol ester of LDL. They can also form chelates that prevent LDL oxidation [26].

Enzymes

Lipoxygenase reaction

Lipoxygenases (LOX, EC 1.13.11.12) Catalyze oxidation of cis, cis-1,4-pentadiene structures of polyunsaturated fatty acids (e.g., linoleic, arachidonic, and linolenic acid). Molecular oxygen in lipoxygenase-catalyzed reactions works as a terminal electron acceptor. Free hydroperoxyl radicals, hydropersonal acids [34] and hydroperoxide are the primary products. Lipoxygenases are thus also able to indirectly modify proteins. The free-radical oxidation of free-thiol groups produces disulphide bonds [35], and the production of reactive cross-linking molecules, like malondialdehydes, have been attributed to the cross-linking ability of lipoxygenases.

Accumulating studies have shown that macrophage 12/15-lipoxygenase has a vital role in circulating LDL oxidation. Before oxidizing LDL, 12/15-lipoxygenase in macrophages has been shown that must be bonded to the receptor-related protein LDL (LRP), the cell-surface receptor. LRP is recommended for selective cholesterol transfer in LDL to the plasma membrane of macrophage

with no endocytosis and degradation of LDL particle [36]. In parallel, the LDL binding to LRP is simultaneous with 12/15-lipoxygenase located in the plasma membrane from the cytosol. 5-lipoxygenases, located on macrophages, also generate leukotrienes, which exhibit strong cardiovascular inflammatory activities and contribute to the development of lesions [26].

Lipid oxidation, as a response to abiotic and biotic stresses, is a common metabolic reaction in all biological systems. Oxylipins are collectively referred to as products derived from processes of lipid oxidation. Initial oxidation of lipids may take place either by chemical reactions or by enzymes [37].

The level of low-density lipoprotein cholesterol is a very important indicator of the occurrence of cardiovascular diseases [29] and it is considered a risk factor that gives an indication of the occurrence and development of the disease as the high level of this factor indicates that the cholesterol transported [38] from the liver to the body tissues will be high, which leads to It increases the risk of developing cardiovascular disease [39], as well as increasing the risk factors for stroke or heart attack [38]. Therefore, the study of this type of protein fats works to know the risk factors of the disease development and the emergence of symptoms [28].

Myeloperoxidase

An enzyme associated with inflammation and oxidation [40] that creates from granules of leukocytes (neutrophils and monocytes) [41]. This enzyme provokes the emergence of white blood cells that prepare reactive materials as well as in their production of (HOCl) acid [42] that has activity within the body's defenses against diseases. (MOP) is present in macrophages within heme, and HOCl secretion is a cell toxin from H_2O_2 peroxide and chloride [43]. That a person possesses this enzyme so that the generation of such an acid oxidizes LDL to a high degree away from the vascular endothelium H_2O_2 \ MOP \ Cl generates a series of secondary reactions (non-radical) [44]. As shown by previous works, cardiovascular disease is increased by higher MPO concentrations [45]. MOP oxidation requires partners such as lipid peroxide or hydrogen peroxide; thus, the effect of MOP on oxidation is less [46].

Glycated

Millard reaction is a chemical reaction between amino acids and reducing sugars [47], which usually requires the presence of heat, and this reaction is the basis for making flavors [48]. The glucose has a covalent binding to amino acids, resulting in stripping of the main albumin site. Lysine is one of the most common amino acids used in the glycation process [49]. A high level of fructose amine was found in LDL and twice higher concentrations of intact protein glucose in the blood of patients. This condition appeared when comparing diabetic patients with non-diabetics [50]. LDL lipid peroxidation is boosted by Glucose via an oxidative pathway [51] in which superoxide is present. The possibility of rapid oxidation of lipoprotein occurs [52] with high blood sugar (diabetes).

Nitric oxide and oxidation mechanism

A more robust antioxidant that vitamin E [53], nitric oxide (NO), is essentially capable of inhibiting but stable, non-physiologically pH oxidizing LDL [54], but the superoxide anion quickly inactivates NO form peroxynitrite ($ONOO^-$) [24], that is a powerful oxidant. Thus, when present in conjunction with superoxide anion, NO plays a prooxidant role [26] and is involved in the LDL oxidation mechanisms [55]. Superoxide anion is produced from the endothelial cell, smooth Muscular Cell and macrophage and peroxynitrite and other reactive intermediate nitrogen can be formed in the artery wall [56], partly leading to LDL oxidation mediated by cells. LDL oxidation can occur with low NO bio-availability and in contrast, with high NO releases of endothelial cells, LDL oxidation can be inhibited. A key antioxidant mechanism in the LDL hydrophobic site, in which the oxidizable lipids' proportion to endogenous antioxidants is higher than the LDL particle surface, can be established by NO vascular cells production and their spread into LDL parts [57]. Thus, NO is an essentially antioxide that has the ability of releasing the superoxide anion through neutrophils and endothelial cells. Superoxide anions and NO both show a slow reaction to other molecules (ascorbate or iron). Thus, each of them easily has reaction to peroxynitrite [26]. NO and superoxide anion formation is occurring simultaneously

in endothelial cells, and therefore, in reaction to endothelial cell stimulations, proximities within the vessel walls are generated. The reactions of NO with superoxide anion with H^+ establishes peroxynitrous (ONOOH) [58] that then shows decomposition into radical hydroxyl acid and radical nitrogen oxide. They are powerful oxidizing agents, and their reactions with unsaturated fatties can initiate and spread lipid peroxidation.

Some disease caused by oxidized LDL (oxLDL)

oxLDL in Hypertension patients

The major risk factor of cardiovascular disease in older people is hypertension that increases oxidative damage. Results of studies [59] found a positive relationship between diastolic blood pressure (DBP) and systolic blood pressure and *in vivo* oxLDL, where higher circulating oxLDL levels were observed in the elderly people at an increased cardiovascular danger when their hypertensive status was increased.

Hypertension through Endothelial Dysfunction, which leads to more atherosclerotic plaque stability and increased chances of coronary problems, particularly in patients at a higher cardiovascular risk, was associated with oxidative stress and LDL oxidation [60, 61].

oxLDL in coronary artery disease

According to research findings, activating the immune system-mediated inflammatory process related to arterial thrombosis stimulates acute coronary syndrome (ACS) [62, 63]. Due to the detection of oxidized LDL (ox) in the plasma of patients with CHD, a significant role is assumed in developing inflammatory processes in all phases in atherosclerotic lesions [64]. Besides, studies have indicated implications of oxLDL in critical and early stages of atherosclerosis, like the expression of adhesion particles, endothelial injury, retention, leukocyte recruitment, and formation of foam and thrombus cells [59, 65]. The present nested case-control prospective research aims at determining whether the risk of acute CHD events can be predicted by plasma oxLDL concentrations. Additionally, it was investigated that whether CHD risk prediction can be improved by measuring oxLDL in plasma beside a standard lipid profile and C-reactive protein (CRP), which is an inflammation-sensitive marker [66, 67].

oxLDL in atherosclerosis patients

Up to 1991, the strength of scientific evidence concerning the low-density lipoprotein oxidation role in the atherosclerosis event recommendation of starting clinical trials by the National Heart, Lung, and Blood Institute. *In vitro* experiments indicated the following points: foamy cell formations are initiated by LDL oxidation as the primary occurrence. Oxidation is observed in LDL lipids in human arterial lesions, with the significant availability of Ox LDL *in vivo* [68]. In addition, atherosclerosis is inhibited in animals by some structurally unrelated compounds, like vitamin E and probucol, because of decreased LDL oxidation [69]. It seems that probucol has higher efficacy in protecting against the formation of the lesions at early stages of disease compared to the lipid-narrowing impact of statin [70]. LDL oxidation in the vascular wall is the initiator of events engaged in the atherosclerotic process, which happens because of the generation of nitrogen species (NOS) and reactive oxygen species (ROS) by endothelial cells. Hence, oxidative modifications are vital in the clinical aspect of coronary artery diseases, like plaque disruption and endothelial dysfunction [71].

oxLDL in Patient with Renal Failure

There are many risk factors for atherosclerosis in chronic kidney failure patients, including oxidative stress, lipid abnormalities, and endothelial dysfunction. Lipid abnormalities chiefly contain high levels of triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), and higher levels of lipoproteins abundant in lipoprotein residues or triglycerides. LDL cholesterol (LDL-C) is disposed to oxidative modification to oxLDL during oxidative stress. The latter works as a chemical attractant to plaques, triggering inflammatory reactions in the arterial wall, like the monocyte adhesion to foamy cells and the monocyte fragmentation into macrophages. The mentioned phenomena cause developing atherosclerotic plaque [72, 73]. Besides, HDL-C provides

protection against development of plaque through reverse cholesterol transporter, which prevents LDL-C oxidation and inhibits cytokine-stimulated expression of adhesion molecules in the surface of monocytes and endothelial cells [74, 75]. According to HDL-C subgroup analysis, there are various physiological roles for HDL-C sub-fractions; The HDL2- C subclass provides protection in reverse cholesterol transport, while the HDL3-C subclass inhibits oxidative damage to the arterial vascular wall. Reduction of C is because of reduction in HDL-C concentration and alterations in its antioxidant activity and composition [76, 77].

oxLDL in Polycystic Ovary Syndrome PCOS

It has been recently found that oxidized low-density lipoprotein (OxLDL) has an elevated level in CAD patients [78], which establishes the OxLDL role in initiating and progressing atherosclerosis. Different works have shown female gender, increased BMI, history of premature cardiovascular disease in family, body fat percent, and exercise below four times weekly as clinical predictors of increased OxLDL levels [79]. Besides, circulating levels of OxLDL predicted CAD with fairly high specificity and sensitivity [80].

oxLDL in non-alcoholic Fatty Liver disease

Along with the global epidemic of obesity, a considerable increase has been witnessed in the incidence and prevalence of non-alcoholic fatty liver disease (NAFLD), as the most widespread liver disease globally [81]. NAFLD is seen in a small but significant proportion of patients with normal BMI. Oxidized LDL is a strong immunogenic molecule, producing antibodies (oxLDL-ab) and causing oxidative stress. Oxidized LDL antibodies/HDL cholesterol ratio might be a remarkable biomarker related to non-alcoholic steatohepatitis NASH, liver fibrosis, and hepatocellular ballooning in lean patients [82].

Also, peroxidation of lipids leads to some degradation end-products that might have the ability of further modulation of the normal properties of lipids and proteins. Additionally, highly reactive aldehydes created in the lipid peroxidation process adjust self-molecules, forming antigenic adducts, called oxidation specific epitopes (OSEs) that are bound by different immune system receptors for alerting the host and promoting their removal for preventing inflammatory impacts [83, 84]. Nevertheless, sterile inflammation is triggered by the OSEs accumulation and their insufficient clearance. OSEs are mainly carried by extracellular vesicles, cells undergoing cell death (apoptosis), and damaged lipoproteins, including OxLDLs. Because of the biological activities of OSEs, OSEs and their immune recognition are engaged in various pathological and physiological processes, such as atherosclerosis [85-87]. Figure 3 indicates the importance and presence of different lipid peroxidation products in the NASH onset. Lipid peroxidation was caused by elevated oxidative stress that might happen through enzymatic reactions, like 12/15-lipoxygenase and myeloperoxidase, as well as non-enzymatic reactions, like reactive oxygen species (ROS). As a result of lipid peroxidation of membrane phospholipids, they are fragmented and breakdown products are generated that can further adjust free amino groups of lipids and proteins and form covalent adducts and oxidation-specific epitopes (OSEs), such as 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), oxidized cardiolipin (OxCL), and phosphocholine on oxidized phospholipids (PC-OxPL). These epitopes are carried by OxLDL, microvesicles, apoptotic cells, and modified proteins. It has been shown that these aspects are present during NAFLD [88].

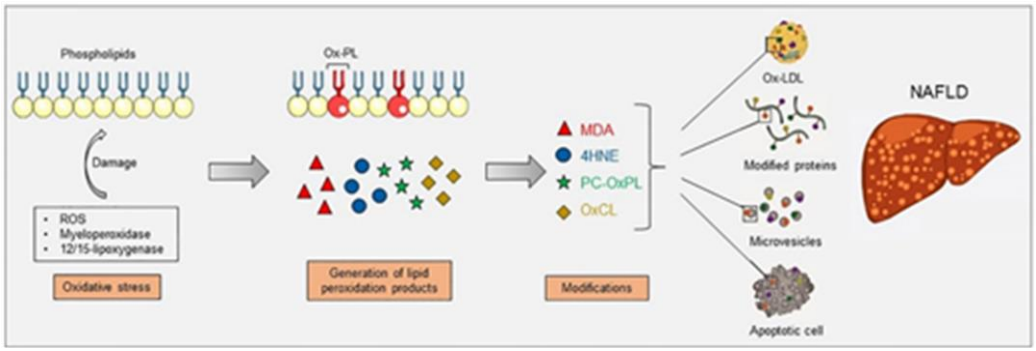

Figure 3. Various lipid peroxidation products in the NASH onset [88]

oxLDL in cerebral infarction

As reported by Uno et al. [89], increased plasma OxLDL is significantly associated with acute cerebral infarction, particularly cortical infarction; an increased OxLDL level indicates oxidative stress in patients with stroke, and it is a helpful independent marker for ischaemic stroke. Besides, it was indicated by Wang et al. [90] that there is an association between higher serum oxLDL/HDL level in transient ischemic attack (TIA) or minor stroke and higher risk of recurrent stroke in 90 days and one year. In industrialized countries, stroke is a significant mortality factor and a source of long-term disability in adults [91, 92]. Thrombotic strokes are characterized by oxidative stress, which leads to oxidative injury and generation of free radicals, resulting in lipid peroxidation promotion. It influences both LDL and other lipoproteins and cellular lipids, such as those in macrophages and the arterial wall [93-95]. oxLDL is increased in neurologic conditions involving cerebral edema formation, such as eclampsia and severe preeclampsia. oxLDL increases cerebral vascular tone dysregulation and blood-brain barrier (BBB) permeability [96].

oxLDL in Patients with Diabetes

People with type 1-2 diabetes are vulnerable to the development of Diabetic retinopathy (DR). However, patients with type 2 diabetes are at a greater risk of prevalence [97]. There is an association between type 2 diabetes and excessive cardiovascular morbidity and mortality [98]. Diabetic nephropathy is a worrying problem of this disease that is the main factor for causing end-stage renal disease in the world. According to evidence, oxidative stress is a major culprit of diabetic nephropathy, and it has been reported that patients with diabetic nephropathy showed elevated levels of ox-LDL immune complexes [99]. If diabetic nephropathy is considered as outcome of the events, it initiates with endothelial cell dysfunction caused by ox-LDL [100, 101]. American research showed that ox-LDL immune complexes triggered the production of collagen IV in mesangial cells, and thus, exerting progressive mesangial thickening in diabetic nephropathy [102]. It has been controversially discussed that autoantibodies to oxLDL Ab as a heterogeneous group of antibodies are either protective or pathogenic. There is also controversy about anthropometric and biochemical measurements associated with elevated levels of these antibodies, particularly in conditions of type 2 diabetes mellitus and interrupted glucose tolerance [103]. As found by the study in [103], there was an increase in anti-oxLDL antibody levels in individuals with interrupted glucose tolerance and type 2 diabetes mellitus, and a positive correlation was indicated with BMI and obesity. As reported by Nakhjavani et al. [104], the serum ox-LDL level elevated with the duration of diabetes, even with maintaining the LDL-cholesterol level of patients at a desirable level.

As hypothesized by Jeremy and Lyons [105], there might be a contribution for ox-LDL to the retinopathy pathogenesis via the primary damage of the blood retinal barrier (BRB) in addition to other metabolic factors observed in diabetes. However, ox-LDL is not the leading cause of BRB damage, and it is involved only when the BRB is leaky. After BRB damage, LDL is modified by LDL extravasation in the extracellular tissue through glycation and oxidation, which increases its toxicity towards retinal cells. Ganjifrockwala et al. [106] showed a significant increase in ox-LDL and a significant reduction in total antioxidant (TAO) in diabetic individuals with retinopathy compared to healthy controls and diabetic patients without retinopathy.

oxLDL support Mycobacterium tuberculosis in macrophages

As demonstrated by recent epidemiological investigations, diabetes mellitus (DM) triples the risk of development of active TB, and it is possible to attribute about 15% of global TB cases to DM comorbidity [107]. Tuberculosis (TB) is an infectious lung disease, which is originated from a bacterium, Mycobacterium tuberculosis (Mtb). This disease is the cause factor of annually more than a million deaths in the world. According to population studies, type 2 DM is a risk factor of Tuberculosis since it triples the risk of development of the disease [108]. oxLDL has been shown as a potential significant DM-related TB-risk factor since it causes lysosomal dysfunction and impairs Mtb infection control

in human macrophages. The immune response towards Mtb, the causative pathogen of TB, is attenuated by metabolic changes. Patients with diabetes mellitus usually suffer from oxidative stress and dyslipidemia that might have a contribution to the oxLDL formation [108, 109].

CONCLUSIONS

It is evident from the research group selected above that irregular metabolism makes an important difference in chemical reactions leading to oxidative stress, cell disease, and death. The process of releasing ROS during oxidative stress is a basic process that arises in the mitochondria through which self-stimulation is increased to increase the damage, and the environment of oxidation and reduction plays physiological roles that lead to the unwanted proliferation of chain reactions and the destruction of mitochondria. That the mechanisms proposed when oxidation of LDL in the laboratory and inside the bodywork to link with the mechanism of lipid peroxidation, in which the superoxide anion is generated, and then a set of complications arise in patients with diabetes or renal insufficiency. Also, a group of infections that stimulate the oxidation of LDL in addition to promoting cases of atherosclerosis.

ACKNOWLEDGEMENTS

The researchers are grateful to the University of Misan and University of Mosul for their unlimited support for scientific work.

Conflict of interests

The author declares no conflict of interest.

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