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LIPID PEROXIDATION: AN OVERVIEW

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ABSTRACT

Lipid peroxidation (LPO) in cellular membranes is associated with changes in physicochemical properties and impairment of protein functions located in membrane environment. Recent studies shows involvement of LPO in biological signaling and various diseases. Lipids are oxidized by three distinct mechanisms: enzymatic oxidation; non-enzymatic, free radical-mediated oxidation and non-enzymatic, non radical oxidation. Lipids containing polyunsaturated fatty acids are susceptible to free radical-initiated oxidation and can participate in chain reactions that increase damage to biomolecules. Polyunsaturated fatty acids (PUFAs) and their metabolites have variety of physiological roles including: energy provision, membrane structure, cell signaling and regulation of gene expression. The present manuscript reviews concept of LPO with emphasis on implication in various diseases.

INTRODUCTION: Lipids are heterogeneous groups of compound having significant role in various functions of body [1], when molecular oxygen reacts with unsaturated lipids catalysed by free radicals (non-enzymatic LPO) or enzymes (enzymatic LPO) [2, 3, 4] turning them rancid due to oxidative deterioration without releasing energy [1, 5] known as lipid peroxidation leads to cell damage by disturbance of fine structures, alteration of integrity, fluidity and functional loss of biomembranes and modifies low density lipoprotein (LDL) to proatherogenic and proinflammatory mediated potentially toxic products [6].

LPO consists of three stages: initiation, propagation and termination [7] proceeded by three distinct methods: free radical-mediated oxidation; free radical-independent, nonenzymatic oxidation and enzymatic oxidation [8] leads to damaging the biomolecules such as nucleic acids, proteins, structural carbohydrates and lipids The initiation phase of lipid peroxidation includes hydrogen atom abstraction by several radical species such as hydroxyl (•OH), alkoxyl (RO•), peroxyl (ROO•) and possibly HO_2• [9]. Polyunsaturated fatty acids (PUFA) in membrane lipids are susceptible to peroxidation because of abstraction of hydrogen atom from a methylene (–CH2–) group containing only one electron.

Moreover, double bond weakens the C–H bonds on the nearby carbon atom facilitating the H• subtraction. The initial reaction of •OH with polyunsaturated fatty acids produces a lipid radical (L•), which in turn reacts with molecular oxygen to form a lipid peroxyl radical (LOO•). The LOO• can abstract hydrogen from an adjacent fatty acid to produce a lipid hydroperoxide (LOOH) and a second lipid radical [10]. Further, reducing agents, such as Fe^{2+}, causes reductive cleavage of LOOH producing lipid alkoxyl radical (LO•). The chain reaction of lipid peroxidation stimulated by both alkoxyl and peroxyl radicals by abstracting additional hydrogen atoms [11]. Further mitochondrial injury can also results in generation of ROS induced by lipid

peroxidation [12]. Lipid hydroperoxide (LOOH) can frequently breakdown into reactive aldehyde products, including malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), 4-hydroxy-2-hexenal (4-HHE) and acrolein, in the presence of reduced metals or ascorbate [12, 13, 14, 15, 16].

Characteristic of lipid peroxidation is the breakdown of polyunsaturated fatty acids to yield smaller fragments, such as aldehydes, classified into three families, on the basis of their structural features: 2-alkenals, 4-hydroxy-2- alkenals and ketoaldehydes [17]. Free radical mediated injury to brain leads to lipid peroxidation, where it directly damages membranes and generates a number of oxidized products. Some of these chemically and metabolically stable oxidised products can be useful as in vivo biomarkers in lipid peroxidation such as isoprostanes (IsoPs) and isofurans (IsoFs), derived from arachidonic acid C20:4n-6 and neuroprostanes (NeuroPs), derived from docosahexaenoic acid C22:6n-3 [18].

Methods of Lipid Peroxidation:

Free Radical-Mediated LPO: The chain mechanism, that is, one initiating free radical can oxidize many molecules of lipids was involved in the free radical-mediated LPO [19]. Porter and his colleagues studied extensively the mechanism involved in free radical-mediated LPO and major reaction includes (1) abstraction of bisallylic hydrogen from polyunsaturated fatty acids to give carbon-centred radicals which rearranges to more stable cis, trans-pentadienyl radicals, (2) addition of oxygen to the pentadienyl radical to give lipid peroxyl radicals, (3) release of oxygen from the peroxyl radical to give oxygen and pentadienyl radicals, which rapidly react with oxygen to give a thermochemically more stable trans, trans form preferentially than cis, trans form and (4) intramolecular addition of the peroxyl radical to the double bond to yield bicyclic prostaglandin-type products [20, 21].

Nonradical, Nonenzymatic LPO: Ozone and singlet oxygen oxidize lipids by nonradical mechanisms [22]. Singlet oxygen oxidizes unsaturated lipids with concomitant double bond migration mainly by ene-reaction to give hydroperoxide, with minor side reactions such as 1, 4-addition to give 1, 4-endoperoxide and 1, 2-addition to give dioxetane, which readily decomposes to yield carbonyl compounds accompanying chemiluminescence. Myeloperoxidase (MPO) is a heme protein secreted by activated phagocytes which reacts with hydrogen peroxide to give hypochlorous acid and hypobromous acid, HOCl and HOBr, respectively, in the presence of chloride and bromide oxidize biological molecules by several mechanisms including both free radical and nonradical pathways [23, 24, 25].

Enzymatic LPO: Lipoxygenase (LOX) and cyclooxygenase (COX) have to be known to oxidise arachidonic acid to hydroperoxyeicosatetraenoic acid (HPETE), prostaglandins, prostacyclin, thromboxane and leukotrienes. COX and LOX oxidize lipids regio-, stereo- and enantio-specifically [26]. Cytochrome P-450 (CYP) was also known to oxidize arachidonic acid to give hydroxyeicosatetraenoic acid (HETE), epoxyeicosatrienoic acid and dihydroxyeicosa-tetraenoic acid [27].

Role of Lipid Peroxidation in various diseases:

Cardiovascular diseases:

Atherosclerosis: Atherosclerosis is characterized by the accumulation of lipids and fibrous connective tissues in the vascular wall which encompasses a complex interaction between inflammatory cells, vascular elements, and lipoproteins [28]. Oxidation of LDL contributes to cell debris core and formation of different products such as lipid hydroperoxides, aldehydes like 4-hydroxynonenal (HNE), oxysterols and lysophosphatidilcholine [29, 30, 31] by modifying lipo-proteins and can cause cardiac cell damage by impairing metabolic enzymes [32]. LDL binds to the HNE covalently and this modification activates macrophages which may contribute to the vascular inflammation leads to atherosclerotic lesions and cytotoxicity [33].

Myocardial Infarction (MI): Myocardial infarction (MI) or acute myocardial infarction (AMI), commonly known as a heart attack, is interruption of blood supply to a part of the heart, causing heart cells to die due to occlusion of a coronary artery followed by rupturing of a vulnerable atherosclerotic plaque, which is an unstable collection of lipids (fatty acids) and white blood cells (especially macrophages) in the wall of an

artery [34]. The extent of damage and death of cardiac myocytes is directly related to consequent morbidity and mortality [35]. HNE may also be responsible for damage to cardiac myocytes that occurs in myocardial infarction by accumulating in myocardial cells during reperfusion injury [36], causing dysfunction and death of cardiac myocytes by a mechanism involving disruption of the actin cytoskeleton and dysregulation of cellular calcium homeostasis [37]. HNE may promote cardiac arrhythmia by inhibiting potassium channels resulting in membrane depolarization and action potential prolongation [38] and cardiac hypertrophy by inhibiting mitochondrial energy-regulating enzyme $NADP^+$-isocitrate dehydrogenase [39].

Stroke: A stroke, also known as a cerebrovascular accident (CVA), is loss of brain function(s) due to disturbance in the blood supply to brain due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism), or haemorrhage (leakage of blood) [40]. Metabolic syndrome (MS) and obesity greatly increases risk for a stroke, which is major cause of morbidity and mortality. For coronary artery atherosclerosis, HNE likely plays roles in the atherosclerotic process in the cerebral blood vessels that are occluded by a clot or rupture during a stroke.

Increased levels of lipid peroxidation/HNE associated with neurons and inflammatory glial cells [41], cause dysfunction and degeneration of neurons by modifying membrane-associated glucose and glutamate transporters, ion-motive ATPases, enzymes involved in amyloid metabolism and cytoskeletal proteins [32]. Levels of HNE are increased in hippocampal neurons prior to their degeneration after transient global forebrain ischemia in a gerbil model of cardiac arrest [42]. Exercise and dietary energy restriction reduce HNE production and may also increase cellular systems for HNE detoxification including glutathione and oxidoreductases [32].

Systemic Lupus Erythematosus: Systemic lupus erythematosus (SLE) is a debilitating autoimmune disease with arthritis, rash, vasculitis, involvement of central nervous system (CNS) and renal and cardiopulmonary systems [43] characterized by the presence of autoantibodies to self-antigens. Increased oxidative damage, mediated by free radicals, is directly result of a change in delicate balance oxidants and antioxidants and an imbalance in pro- and anti-inflammatory molecules, with elevated levels of malondialdehyde, conjugated dienes 4-HNE and decreased levels of antioxidant enzymes (extracellular SOD, catalase and glutathione peroxidise) [44]. Suryaprabha et al. reported the elevated levels of superoxide and hydrogen peroxide production by peripheral leucocytes in SLE patients without any elevated levels of malodialdehyde levels measured by thiobarbituric acid assay [45].

Erythrocyte dysfunction and Aging: Erythrocyte aging is senescence of red blood cells, lacking organelle for protein synthesis and mature erythrocyte is incapable of self-repair, reproduction and carrying out functions performed by other cells [46]. Lipid peroxidation represents a significant source of erythrocyte dysfunction and aging [47]. The lipid derived aldehydes like 4-hydroxy-trans-2-nonenal (HNE), abundant and toxic, are metastable and diffuse from their site of origin to propagate oxidative injury by acting as “toxic second messengers”.

The electrophilic nature of α, β unsaturation in HNE renders it highly reactive with cellular nucleophiles such as glutathione, cysteine, lysine and histidine of proteins and with nucleic acids [12, 48, 49]. High concentrations of HNE are cytotoxic, whereas lower concentrations of HNE modulate cell proliferation and gene expression, inhibit the synthesis of nucleic acids and proteins, stimulate neutrophil chemotaxis and modulate platelet aggregation [12]. Erythrocytes are potential targets of lipid peroxidation products [50] like HNE which accumulate in the erythrocytes [51] and cause covalent modification of the intrinsic proteins [52] and red cell lyses [1].

Behçet’s Disease: Behçet’s disease (BD) is a chronic multisystemic disorder which is characterized by a relapsing systemic inflammatory process, particularly affecting the vascular bed. Various reports showed that various functions of polymorphonuclear (PMN) leukocytes in peripheral blood, such as chemotaxis, phagocytosis and superoxide radical anion (O_2^-) generation are increased in Behçet’s disease [53, 54], affecting skin, mucous membranes, eyes, joints, central nervous system and blood vessels [55, 56]. Different factors involved in the pathogenesis of this disorder includes genetic factors, viral infections,

allergies to bacteria and several immunologic abnormalities [57] and increased levels of oxygen free radicals plays role in tissue damage in BD [58, 59, 60]. Oxygen free radicals can lead to lipid peroxidation reactions as a result of which malondialdehyde (MDA) is produced [60, 61].

Neurodegenerative Disorders:

Amyotrophic Lateral Sclerosis (ALS): Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects both upper and lower motor neurons [62]. Reactive intermediates such as 4-hydroxy-2-nonenal-histidine (HNEH), crotonaldehyde-lysine (CRAL), *N* -(carboxymethyl) lysine (CML), pentosidine, *N*e -(carboxyethyl)lysine (CEL), argpyrimidine, pyrraline and imidazolone [12] modify proteins to form advanced glycation and products (AGEs) or advanced lipoxidation end products (ALEs) [63]. Lipid peroxidation and protein glycoxidation are enhanced in the spinal cord motor neurons and glial cells and formation of intermediates in these abnormal reactions is implicated in motor neuron degeneration [64].

Alzheimer's disease: Alzheimer's disease is characterized by the degeneration of neurons in brain regions involved in cognition (hippocampus, entorhinal cortex, frontal cortex and associated structures) and emotional behaviors (amygdala, prefrontal cortex, hypothalamus and others). The abnormal production and aggregation of amyloid β-peptide (Aβ) is believed to be a pivotal event in the disease process [65]. Elevated levels of HNE in association with Aβ plaques and neurofibrillary tangles (degenerating neurons with intracellular aggregates of the microtubule-associated protein tau) [66, 67, 68] in the cerebrospinal fluid, is considered as potential biomarker of this disease [69].

Exposure of Aβ to cultured neurons results in lipid peroxidation and HNE production which impairs the function of membrane ion-motive ATPases and glutamate and glucose transporters which renders neurons vulnerable to excitotoxicity and apoptosis [70, 71, 72, 73]. Inflammatory processes involving activation of Toll-like receptors (part of the innate immune system) may mediate the death of neurons downstream of Aβ and HNE [74].

Parkinson's disease: Parkinson's disease (PD) is characterized by selective degeneration of dopaminergic neurons of the substantia nigra, resulting in bradykinesis, tremor and rigidity. Free-radical generation and lipid peroxidation causes oxidative stress by activation of phosholipase in substantia nigra, plays important role in the pathogenesis of this disease, supported by the fact that $cPLA_2$ null mice are resistant to 1-methly-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced nephrotoxicity.

The MPP^+ metabolite of MPTP is taken up by the nigrostriatal neurons causing neuronal death by inhibiting mitochondrial oxidative phosphorylation [75]. In PD, excessive reactive oxygen species (ROS) results from accelerated metabolism of dopamine by monoamine-oxidase-B.

Marked increase in 8-hydroxy-2'-deoxyguanosine (a hydroxyl radical-damaged guanine nucleotide commonly used to evaluate oxidative damage to DNA) and significant increase in several markers of lipid peroxidation in PD brain regions were found [76].

Obsessive-Compulsive Disorder: Obsessive-compulsive disorder (OCD) is a common, disabling disorder characterised by obsessions and/or compulsions that are egodystonic [77].

The fronto-striato-pallidothalamo-loop circuitry of the brain provides a unifying framework for understanding processes that control cognition, decision-making, planning of complex behavioral strategies and neuropsychiatric symptoms and defect in this circuit has been suggested by the derangements in cognitive functions, emotional state, executive and decision making functions in OCD patients [78]. Abnormal catecholamine metabolism in the brain cells might produce increased free radical generation in OCD patients [79].

Chakraborty *et al*. reported significantly higher mean values for serum TBARS in OCD patients than controls and a strong positive correlation between the lipid peroxidation marker TBARS and the disease severity indicator Yale Brown Obsessive Compulsive Scale (YBOCS) was found among cases [80].

Diabetes mellitus: Diabetes Mellitus (DM) is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [81]. Diabetes mellitus is a state of increased oxidative stress resulting in higher production of reactive oxygen species (ROS), such as superoxide radical, hydroxide radical, hydrogen peroxide (H_2O_2) and/or deficiency in the antioxidant defence systems [82, 83] which has been attributed to protein glycation and/or glucose auto-oxidation owing to a hyperglycemic environment [84].

Kesavulu *et al*., investigated the relationship between serum lipids, lipoproteins, lipid peroxides [thiobarbituric acid reactive substances (TBARS)] and erythrocyte antioxidant enzymes [catalase (CAT), glutathione peroxidise (GPx) and superoxide dismutase (SOD)] in non-insulin-dependent diabetic patients with and without coronary heart disease (CHD), and a comparison was made for all the above parameters with non-diabetic patients with CHD. Lipid peroxide concentrations were significantly increased in diabetic patients and non-diabetic patients with CHD compared to normal and diabetic patients with CHD had higher levels of TBARS, increased total cholesterol and LDL-cholesterol compared to those diabetics without CHD.

Among the erythrocyte antioxidant enzymes, CAT activity was increased, GPx activity was decreased and no change was observed in SOD activity in both groups of diabetic patients and non-diabetic patients with CHD compared to those in controls [85].

Obesity: Obesity promote disease by increasing oxidative damage to proteins, lipids and DNA as the result of a combination of increased free radical production and an impaired ability of cells to detoxify the radicals and repair damaged molecules. By covalently modifying membrane-associated proteins, the membrane lipid peroxidation product 4-hydroxynonenal (HNE) plays sinister roles in the metabolic syndrome and associated disease processes, damage pancreatic β cells and impair the ability of muscle and liver cells to respond to insulin [32]. Increased oxidative damage to cellular constituents (proteins, lipids and DNA) and increased inflammation as indicated by elevated levels of tumor necrosis factor (TNF), interleukin-1b and other proinflammatory cytokines are two systemic alterations involved in the obesity and metabolic syndrome (MS) [86, 87, 88]. Oxidative stress induces the production of inflammatory cytokines and the cytokines in turn induce free radical production [89].

Cancer:

Hodgkin's disease: Hodgkin's disease (Hodgkin's Lymphoma) is a type of lymphoma i.e. cancer originating from white blood cells called lymphocytes, named after Thomas Hodgkin, who first described abnormalities in the lymph system in 1832 [90, 91], characterized by the orderly spread of disease from one lymph node group to another and by the development of systemic symptoms with advanced disease. Gu¨ ven et al. demonstrated increased erythrocyte superoxide dismutase (SOD) activity and decreased erythrocyte and plasma Glutathione peroxidise (GPX) activities in patients with Hodgkin's disease.

Superoxide anion radicals converted rapidly to hydrogen peroxide by SOD cross cellular membranes and interact with superoxide anion radicals to produce the hydroxyl radical to react with biological molecule in its vicinity and damage proteins, cause DNA strand breakage, and initiate lipid peroxidation. Significantly higher concentrations of MDA in plasma as well as in erythrocytes, higher level of SOD in erythrocyte and lower level of GPX in plasma and erythrocyte as compared to the control group were also reported [92].

Skin Cancer: Skin exposure to ultraviolet (UV) radiation induces dermal changes such as erythema, skin aging, and skin cancer [93]. The UVA (320–400 nm) region is a major component of sunlight that produces oxidative stress by interaction with intracellular chromophores [93]. Reactive oxygen species (ROS) such as singlet oxygen and superoxide anion promotes biological damage in exposed tissues via iron-catalyzed oxidative reactions [94].

ROS initiate oxidative damage in membrane lipids resulting in lipid radicals which propagate peroxidation process leading to accumulation of lipid hydroperoxides [95, 96]. UVA exposure induces the synthesis of MMP-1, the interstitial collagenase which is responsible for the degradation of dermal collagen [97, 98, 99], mediated by singlet oxygen [100] and in parts by

proinflammatory cytokines interleukin-1 and 6 [101] and its increased activity is observed in tumor progression, metastasis, and cutaneous photoaging in human skin [97, 98, 99]. Polte and Tyrrell clearly demonstrated a direct role of iron in UVA-induced transcriptional activation of MMP-1[102] where iron leads to formation of specific iron (II)/iron (III)/O2 complexes, which have decisive role in initiation of lipid peroxidation processes and involved in direct reactions with unsaturated fatty acids or lipid peroxides, producing peroxyl radicals that lead to propagation of lipid peroxidation [103].

Chronic Liver Diseases: Oxidative stress plays a role in the pathogenesis of a certain liver diseases such as alcoholic liver disease, metal storage disease and ischemia/reperfusion injury and hepatic fibrosis Development of fibrosis and cirrhosis are major complication of chronic hepatitis B. Lipid peroxidation can be detected in situ and commonly occurs in severe chronic hepatitis B and related to active necro-inflammatory change of the liver and contribute to the progression of the disease in chronic hepatitis B [104].

Cholestatic Liver Injury: Cholestatic liver injury is a very common feature of chronic liver diseases where the accumulation of cytotoxic bile acids plays a pivotal role in determining liver necrosis and then in sustaining the development of liver fibrosis [105]. The mechanism involved in bile acid cytotoxicity includes detergent properties [106], alteration of intracellular Ca 2^+ homeostasis [107], ATP depletion and mitochondrial damage [108].

Various studies suggested the involvement of reactive oxygen species (ROS) and free radical reactions in the pathogenesis of cholestatic liver injury and evidences supporting this include : deleterious effect of a high-fat diet as well as the detection of lipid peroxidation in mitochondria isolated from the liver of bile duct ligated rats [109, 110] ,detection of lipid peroxides in erythrocytes and in plasma of children affected by chronic cholestasis [111, 112], a possible pro-oxidant effect of hydrophobic bile acids against isolated hepatocytes [113], a decrease in antioxidant defences in the liver of bile duct ligated rats [114].

Alopecia Areata: Alopecia areata (AA) is an autoimmune [115], disabling chronic inflammatory disorder of the hair and nails [116] whose severity ranges from patchy loss of scalp hair to the loss of all scalp hair (alopecia totalis; AT) or all scalp and body hair (alopecia universalis; AU) [117]. AA is characterized by an inflammatory cell infiltrate surrounding the hair follicle which is associated with damage to hair follicle and subsequent change in the normal keratinisation [118].

Various factors may play role in the pathogenesis of AA like cytokines including interleukin I (IL-I) alpha, IL-I beta and tumor necrosis alpha (TNF-α) [119] which is synthesized and released into the extracellular milieu by immune and non immune cells during inflammatory processes leading to stimulation of intracellular production of mitochondrial ROS [120] initiating an increase in the cellular antioxidant defense mechanism, i.e. an increase in SOD and GSH-Px activity [121].

The levels of TBARS in scalp of patients with AA were significantly higher than those of controls; the mean levels of TBARS, SOD and GSH-Px in early phase of disease were increased 2-fold as compared with late phase of the disease and also high SOD and GSH-Px activities in the scalp of patient with AA. These high levels could not protect the patients against the reactive oxygen species, because lipid peroxidation could not be lowered in AA patients [115].

Acute Respiratory Distress Syndrome: Acute and chronic organ failures, such as acute respiratory distress syndrome (ARDS), liver failure due to cirrhosis, heart or kidney failure are caused by inflammatory processes. Oxidative metabolites are known as potent triggers of inflammatory diseases leading directly to severe cell damage, accompanied by impaired antioxidative capacities. Lichtenstern *et al*., reported that acute respiratory distress syndrome (ARDS) patients showed significantly higher levels in MDA concentrations and blood concentrations of hexanal and propanal, specific by-products of lipid peroxidation, than controls. Malondialdehyde (MDA) is the prototype of these indicators and served in a huge number of studies for detection of LPO [122].

Dental Diseases: The role of free radicals (salivary MDA) in the dental condition such as oral submucous fibrosis, candidasis, dental caries, periodontal disease, leukoplakia and oral cancer has been reported [123]. A study in a baby hamster kidney cell line and its

polyomavirus transformed malignant counterpart, reported high level of lipid peroxidation in transformed cells and low alpha tocoferol content, suggesting that the level of lipid peroxidation is increased in the malignant state, in precancerous condition, oral cancer and periodontal diseases [124]. High level of MDA in periodontitis, leukoplakia, oral submucosis and cancer were found as compared to controls, indicating a role of free radical in pathogensis of precancerous condition lesion, cancer and periodontal disease [123].

CONCLUSION: Membrane phospholipids containing polyunsaturated fatty acids are particularly susceptible to oxidation and can contribute in chain reactions that amplify damage to biomolecules. Lipid peroxidation often occurs in response to oxidative stress, and a great diversity of phospholipid oxidation products and aldehydes is formed when lipid hydroperoxides break down in biological systems and these products exert cytotoxic and genotoxic effects. In conclusion, the aim of this review is to demonstrate process of lipid peroxidation occurring in PUFA making toxic metabolites, leading to free radical generation, which are involved in various diseases. There is a vital need to target these toxic metabolites in order to reduce the rising burden of diseases caused due to lipid peroxidation process.

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