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Role Of Reactive Oxygen Species (ROS) In Aging And Aging-Related Diseases.

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ABSTRACT

Reactive oxygen species (ROS) are common by-products of many natural oxidative biochemical processes in living cells. They are generated by breaking of a covalent bond of molecules. Conversely, environmental, lifestyle and pathological conditions also cause oxidative stress, a condition when free radicals production overwhelm antioxidant capability to regulate them by the cells which leads to various diseases including aging. Increased in reactive oxygen species (ROS) is known to cause diabetic macro- and microvascular complications in human. Oxidative stress also causes atherosclerosis, a disease of the arteries involving a local thickening of the vessel wall which leads to cardiovascular disease. Furthermore, both normal and pathological aging have been associated with increased accumulation of free radicals may affect the ability to cope with cellular damage induced by ROS in the living cells. Hence, in this mini review, we summarize the role of free radicals in cardio metabolic diseases and aging process.

Keywords: Antioxidant, free radicals, cardio metabolic diseases, aging

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INTRODUCTION

Reactive oxygen species (ROS) and other free radicals *R*• are common by-products of many oxidative biochemical processes in cells. They are generated by homolytic cleavage of covalent bond of molecules or imbalance of electron in the stable molecule [1]. However, environmental, lifestyle, and pathological conditions cause oxidative stress, a condition when free radicals production overwhelm antioxidant capability to regulate them, adversely are capable of damaging biologically relevant biomolecules. The imbalance of reduction-oxidation species are one of the processes that regulates gene expression in many pathological conditions. Oxidative damage to different cell types and its biomolecules such as DNA, proteins, and lipids that have been associated with development of chronic diseasesincluding aging, cancer, inflammatory joint disease, asthma, senile dementia, degenerative eye diseases, and cardiovascular diseases such as ischemic heart disease, atherosclerosis, cardiac arrhythmia, hypertension, and diabetes [2]. Noteworthy, population studies have reported that up to 80% of cardiovascular disease, 90% of type II diabetes are caused by oxidative stress[3].Hence, this mini review was summarized the role of free radicals incardio metabolic diseases and aging process**.**

Oxidative Stress inDiabetic Complications

Increased in reactive oxygen species (ROS) is known to cause diabetic macro- and microvascular complications[4-6]. ROS induces auto-oxidation of glucose and shifts in redox balances from shunting glucose to the polyol pathway, which increase the vasculaturesusceptibility to oxidative damage. It is apparent that hyperglycemia-induced oxidative stress in the pathogenesis of diabetic complications (Figure 1)[7]. Hyperglycemia induces oxidative stress that increases generation of ROS or diminishes the production of antioxidants that can lead to increased oxidant-derived vascular injury(3) Chronic hyperglycemia increases oxidative stress, significantly modifies the structure and function of proteins and lipids, and induces glycation of proteins, leading to the accumulation of advanced glycation end products (AGEs), one of the key sources of free radicals strongly contributed to development of diabetes complications.These glycation products may increaseconcentration of the superoxide radical and H2O2, activate phagocytes, and reduce glutathione[8]. Accumulation of AGEs causes formation of cross-links between molecules in the basement membrane of the extracellular matrix. In addition, ROS increases production of endothelial nitric oxide synthase (eNOS) and superoxide activity, and stimulates intracellular signalling such as protein kinase C (PKC), c-Jun-N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK). ROS also activates transcription factors such as forkhead box O (FOXO) and nuclear factor kappa-B (NF-kB) through regulation of the gene transcription of inflammatory and antioxidant genes [9]. On another hand, accumulation of AGEs in the kidney induces transforming growth factor (TGF)-β gene expression via protein kinase C (PKC). High glucose activates PKC which increase levels of ROS in diabetic glomeruli, causing augmentation of mesangial expansion, basement membrane thickening, and dysfunction of endothelial cells, leading to vascular damage[10-12]. Hyperglycemia elevates intracellular ROS by many converging pathways by activating an array of inflammatory response of immune factors. Increased ROS intensifies the production of pro-inflammatory cytokines, which further promote the production of free radicals. ROS productioncan be stimulated via increased polyol pathway, AGEs formation, NADPH oxidase and activation of PKC, to activate Inflammatory components in diabetic kidney. ROS provokes inflammatory activity through activation of PKC, mitogen activated protein kinase MAPK, NADPH oxidase, and nuclear factor-κB, and upregulates TGF-β1 and fibronectin pathways. Oxidative stress also enhances expression of growth factor such as VEGF, a protein factor secreted by the podocytes and the mesangial cells of the kidney, which interferes with the phosphoinositide 3-kinase/protein kinase B (Akt/PKB) pathway and modulates the expression of endothelial nitric oxidesynthase. VEGF elevates the level of intracellular ROS by stimulating the generation of peroxynitrite, thereby deterioratingvascular damage [12-15].In addition, hyperglycemia promotes pre-mature vascular aging, thereby increases risk of diabetes-related vascular complications [16]. Several ROS are involved in the development of age-associated changes in the vascular wall [17]. Aging vasculature produces excess reactive oxygen species (ROS), superoxide and hydrogen peroxide that compromise vasodilatory activity of nitric oxide (NO) and facilitate the formation of the free radical, peroxynitrite. In addition, increased oxidative stress mediated by erythroid-2-related factor-2 (Nrf2) and downregulation of mitochondrial manganese superoxide dismutase (SOD2) are known to cause vasculardamage. This is manifested by chronic low-grade inflammatory phenotype leading to defective endothelial vasodilation. The redox-sensitive transcription factor, nuclear factor-B (NF-kB), is upregulated in vascular cells. This chronic NF-B activation is contributed by increased angiotensin-II signalling and down-regulated sirtuins and precludes adequate cellular response to acute ROS generation. Another mechanism

known to be played by oxidative stress is through reduction of NO in endothelial cells [18], whichresults ingrowth arrest and cell death[19, 20]. Increased oxidative stress and ROS production have been detected in different vascular beds from animal models, that includes rat aorta [87-89] and coronary arteries [90] and mouse aorta [91], inducing a decreased endothelial NO-bioavailability. Autophagy impairment increasesmitochondrial superoxides overproduction in the mitochondrial of endothelial cells. Superoxideactivates five major pathways: polyol pathway flux,increased formation of advanced glycation end products (AGEs), increased expression of the AGE receptor and itsactivating ligands, activation of protein kinase C isoforms, and overactivity of the hexosamine pathway [18], and inactivatestwo critical anti-atherosclerotic enzymes, eNOS and prostacyclin synthase.Through these pathways, oxidative stress alters signalling and transcription factor in the cellular microenvironment leading to vascular dysfunction over time.

Oxidative stress provokes epigenetic changes in diabetic complications

Recent research has found that oxidative stress augments posttranslational histone acetylation and functional changes in transcription for genes in the region of the acetylated histone[21]. Overproduction ofhistone acetyltransferase p300 has been implicated in activation of vasoactive genes. Increased expression and activity of p300 are observed in endothelial cells treated in high glucose, with parallel increased expression of VEGF, FN, and ET-1 [22]. Increased acetylation of histone H3 subunit and complexes of p300 and NF-kB at the promoters of ET-1 and FN, accounts for the HAT and co-activator mechanisms of p300-mediated gene activation. DNA repair enzymes ERCC1 and ERCC4 increase FN expression in a p300-dependent manner [23].Moreover, diabetic nephropathy and cardiomyopathy [24, 25]. MAPK, PKC, and Akt pathways have been shown tomediate overexpression of p300, and all can be activated inresponse to oxidative stress [22]. Evidence from rat cardiomyocytes suggested that oxidative stress stabilizes p300 levels and activity [26]. In addition, DNA damage-induced PARP activation secondary to oxidative stress has been reported in diabetic cardiomyopathy, retinopathy, and neuropathy [27-29]. Therefore, oxidative stress increases HAT activity in chronic diabetic complications, thus regulating the balance of gene activation and promoting expression ofgenes implicated in diabetes.

Oxidative stress and mitochondria dysfunction

Diabetes causes mitochondrial superoxide overproduction in the endothelial cells. Increased superoxide production activates cellular signaling pathways and transcription factors such as protein kinase C (PKC), c-Jun-Nterminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), forkhead box O (FOXO), and nuclear factor kappa-B (NF-kB). Mitochondria is predominant intracellular source of superoxide production [103]. Superoxide mainly produced by complexes I and II is rapidly dismutated by manganese superoxide dismutase (SOD2) in mitochondrial matrix to form H2O2 that may leave mitochondria due to its neutral conformation. ROS impairs vasodilation [107], which interferes with aortic endothelium-dependent relaxation [108]. Elevated level of mitochondrial ROS also causes arterial stiffness [109]. p66Shc adaptor protein seem to regulate mitochondria-derived oxidative stress. p66Shc[30]. Overexpression of p66Shc reduces NO production in endothelial cells. These evidences and the implication of p66Shc in cardiovascular diseases point to this protein as a key factor in arterial dysfunction and cardiovascular disease. An additional important link between mitochondrial oxidative stress and cardiovascular disease is the induction of programmed cell death. The available evidence suggests that oxidative stress causes an increased rate of endothelial apoptosis[31]. Furthermore, recent studies show that mitochondria-derived ROS, in addition to causing oxidative damage, play an important role in activating numerous redox-sensitive transcription factors, including NF-B and AP-1[32, 33]. Activation of another redox sensitive factor, kruppel-like factor 4 (KLF-4) could be responsible for up-regulation of mitochondrial SOD isoform (MnSOD). In addition, damage to mitochondria can reduce the capacity to generate ATP. A lower activity of complex I and complex IV secondary to reduced protein expression of certain complex components has been shown in animal models, and an impaired electron transport chain function also causes an increase in ROS generation. The electron chain transport induces the production of $O_2^{\cdot-}$ as an end-product from electron uncoupling, followed by a reduction in oxygen to form this free radical. Moreover, mitochondria can also generate $HO^{\cdot}$, H_2O_2, and $NO^{\cdot}$, capable of causing deleterious effects to other proteins or the DNA[34]. The nervous system seems to be particularly vulnerable to oxidative stress damage due to a high energetic demand and elevated lipids content. It has been proved that hyperglycemia induces a dosedependent effect on cleavage of caspases through ATP depletion. Hyperglycemia generates ROS coupled with hyperpolarization of the mitochondrial membrane potential (MMP), followed by mitochondrial membrane depolarization, which is temporally related to an increase in

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ADP:ATP ratio and an absolute decrease in ATP levels. This in turn is coupled with cytochrome *c* release from the intermitochondrial membrane space and cleavage of caspases, resulting in dorsal root ganglion apoptosis.

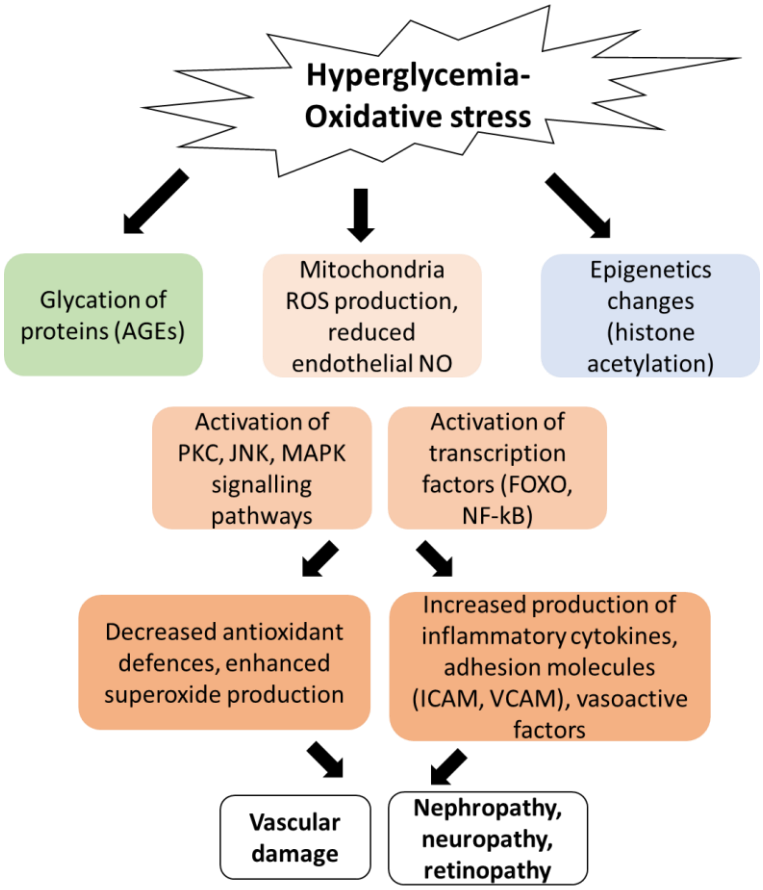

Figure 1: Oxidative stress in diabetes complications. Hyperglycemia-induced oxidative stress activates multiple signalling pathways in the endothelial cells, (protein kinase C (PKC), c-Jun-N terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and increases transcription factors (nuclear factor kappa-B (NF-B), forkhead box O (FOXO).Activation of signalling cascades decrease antioxidant defenses, which increases susceptibility to further damage from oxidative stress. Furthermore, these signalling pathways result in increased production of vasoactive factors, adhesion molecules and pro-inflammatory cytokines, which initiate vascular damage in target organs. Finally, formation of advanced glycation products (AGEs) and epigenetic mechanisms such as histone acetylation can be triggered by oxidative stress.

Oxidative stress in cardiovascular disease

Under physiological condition, native or non-oxidized LDL uptake is under high homeostatic regulation. Increased accumulation of oxidized LDL and lipid peroxidation products and presence of antibodies against oxidized LDL have been observed in the blood of patients with atherosclerotic disease [35, 36]. Oxidative stress causes atherosclerosis, a disease of the arteries involving a local thickening of the vessel wall, mainly evident in mid-sized muscular arteries [37]. Free radicals causes formation of thrombus at the site of the plaque, occludes blood vessel lumen, leading to stroke or myocardial infarction. Arterial endometrium injury triggers emigration of monocytes into the arterial inner core (tunica intima). The fatty streak develops by aggregation of foam cells in the subendothelial portion of the vessel wall, is the earliest event in atherosclerosis. These lipid-laden foam cells contain large deposits of oxidized LDL cholesterol (ox-LDL) and lipid peroxidation by-products, are precursors of atherosclerotic lesion.18 Oxidized-LDL induces cellular injury through sequential of events: (1) increased transmigration of circulating monocytes into the vessel intima by the chemoattractant force of oxidized LDL [38] (2) enhanced rates of oxidized LDL uptake and degradation by the macrophage through the receptor [39] (3) oxidation of the LDL particle inhibits macrophage exodus from

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the artery [40] (4) increased aggregation of foam cells to become fatty steak, and (5) accumulation of oxidized LDL and atherosclerotic lesions (FIGURE 2).

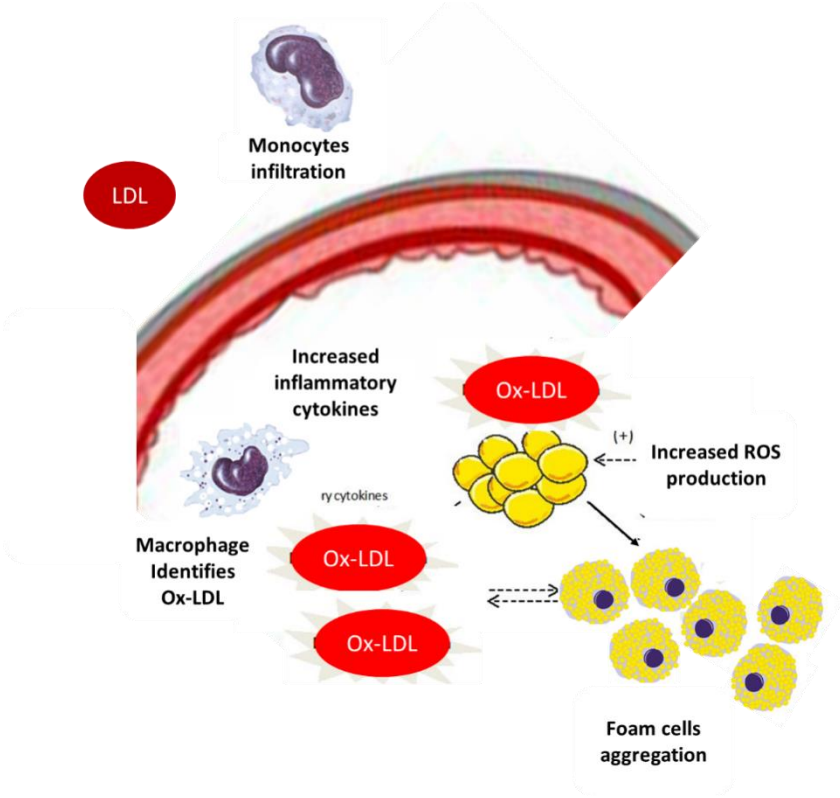

Figure 2: Proposed scheme of fatty streak development through LDL oxidation. Lipid peroxidation increases concentrations of reactive oxygen species (ROS). *The most reactive species,* hydroxyl radical ($OH^{\cdot}$) attack LDL.Oxidation of LDL generates a lipid peroxyl radical ($LOO^{\cdot}$), andinitiates oxidation attacks cycle. Lipid peroxidation begins when a methylene group (CH2) of the LDL is attacked by a ROS tolipidperoxyl radical ($LOO^{\cdot}$) oxidizes LDL in the cell membrane to ox-LDL. Ox- LDL particle is identified by the receptor of the macrophage and engulfed, leading to foam cell formation. Through this cycle, a single initiating ROS can result in the conversion of hundreds of fatty acid side chains into lipid peroxides that alter the integrity and biochemical function of cell membranes.

Oxidative stress in Aging

Free radicals (ROS) causes oxidative damage to mitochondria and mitochondrial DNA (mtDNA) [41, 42]. Oxidative damage affects replication and transcription of mtDNA and compromises mitochondrial function, which in turn, enhances ROS production and mtDNA damage cycles. Mitochondria are the major producer of ROS in cells, and the bulk of mitochondrial ROS is generated at the electron transport chain [43, 44]. Electrons leak from the electron transport chain directly to oxygen, producing short-lived free radicals such as superoxide anion (O2−) [42, 45]. O2 − can be converted to nonradical derivatives such as hydrogen peroxide (H2O2) either spontaneously or catalyzed by superoxide dismutase (SOD) [32, 46-48]. H2O2 is relatively stable and membrane permeable, it can be diffused within the cell and be removed by cytosolic antioxidant systems such as catalase, glutathione peroxidase, and thioredoxin peroxidase [49, 50]. Other than mitochondrial respiration, a number of cytosolic enzymes are able to generate ROS [51]. The nicotinamide adenine dinucleotide phosphate (NADPH) oxidases are a group of plasma membrane-associated enzymes found in a variety of cell types [52]. The function of NADPH oxidases is to produce superoxide from oxygen using electrons from NADPH [53]. Once they are produced, ROS react with lipids, proteins, and nucleic acids causing oxidative damage to these macromolecules [54-58]. ROS readily attack DNA and generate a variety of DNA lesions, such as oxidized DNA bases, abasic sites, and DNA strand breaks, which ultimately lead to genomic instability [59]. 7,8-dihydro-8-oxodeoxyguanosine (8-oxo-dG) is one of the most abundant and well-

characterized DNA lesions caused by ROS [60]. It is a highly mutagenic lesion that results in G: C to T : A transversions[61].

The Free Radical Hypothesis of Aging (Oxidative Stress Theory of Aging) indicates that aging affects the body's ability to cope with oxidative stress that occurs throughout the lifespan. Indeed, both normal and pathological aging have been associated with increased accumulation of free radicals may affect the ability to cope with cellular damage induced by ROS [62]. Increased ROS production by mitochondria and increased 8-oxo-dG content in the mitochondria DNA (mtDNA) are frequently detected in aged tissues [63-67], suggesting progressive accumulation of oxidative DNA damage is a critical factor in aging [68-70]. Oxidative stress maycause lipid and protein peroxidation, increases in DNA oxidation products, and deficits in calcium regulatory mechanisms. Free radicals impair mitochondrial function by compromising specific inner mitochondrial membrane processes such as malate transport. Post transcriptional modifications appear to be involved in loss of these carriers attributed to chronic oxidative stress. In addition, declined mitochondrial membrane potential may reduce the energy supply from the mitochondria and affect protein synthesis. Studies in isolated mitochondria have shown that oxidative stress causes inhibition of respiration, affecting mitochondrial membrane potential. Acute oxidative stress increases oxidation of mitochondrial glutathione and causes mitochondrial swelling [31, 71, 72] .

CONCLUSION

In conclusion, oxidative stress play an important roles in diabetic, cardiovascular disease and aging. Moreover, both normal and pathological aging have been related with the accumulation of free radicals in the living cells. Hence, future research on the antiaging activity and aging related diseases should be targeted the prevention of accumulation excessive amount of free radicals in the cells which normally leads to the cardio metabolic diseases and aging process.

CONFLICT OF INTEREST

Authors declare no conflict of interest in the present work.

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