# Lipid Peroxidation and Age-Associated Diseases-Cause or Consequence?: Review

## Lipid Peroksidasyonu ve Yaşa-Bağlı Hastalıklar-Sebep mi, Sonuç mu?

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**ABSTRACT** Aging is progressive and deleterious process in many aspects common to all living organisms. In humans, development of various diseases, such as neurodegenerative diseases, cardiovascular diseases, some forms of cancer, metabolic disorders, diabetes, certain autoimmune and bone diseases, is proportional to aging. Therefore, it seems that excess in production of reactive oxygen species causing oxidative stress and lipid peroxidation plays important role in aging, homeostasis and initiation of age-associated diseases. Hence, oxidative stress and lipid peroxidation could be considered both as causative for particular age-associated diseases as well as cofactors of aging. However, constant but moderate oxidative stress might have beneficial impact upon increment of antioxidative capacities thus preventing initiation of age-associated diseases and extending aging.

**Key Words:** Aging; oxidative stress; lipid peroxidation; 4-hydroxynonenal

**ÖZET** Yaşlanma tüm yaşayan organizmalarda ortak olan progresif ve zarar verici bir süreçtir. İnsanlarda nörodejeneratif hastalıklar, kardiyovasküler hastalıklar, bazı kanser çeşitleri, metabolik bozukluklar, diyabet, bazı otoimmün ve kemik hastalıkları gibi rahatsızlıkların gelişimi yaşlanma ile ilgilidir. Lipid peroksidasyona ve oksidatif strese neden olan reaktif oksijen türlerinin üretiminde artma yaşlanmada, homeostasis ve yaşa bağlı hastalıkların başlamasında önemli rol oynar. Oksidatif stres ve lipid peroksidasyon bazı yaşa bağlı hastalıkların nedeni olabilir. Buna rağmen orta dereceli sabit bir oksidatif stres antioksidatif kapasite artışı ile yaşa bağlı hastalıkların başlamasını ve aşırı yaşlanmayı önlemesiyle de yararlı olabilir.

**Anahtar Kelimeler:** Yaşlanma; oksidatif stres; lipid peroksidasyonu; 4-hidroksinonenal

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Aging is an inevitable and progressive degeneration of biological functions that is universal among living organisms. There are many different theories of aging but one of the most commonly accepted is the "free radical theory" of aging proposed by Harman in 1956. Briefly, the theory states that the aging process results from the accumulated damage caused by reactive oxygen species (ROS), highly reactive molecules that, among other sources, are normal by-products of cellular metabolism.[1-3] Thus paradoxically, as oxygen is needed for our living it can also be detrimental for us. If ROS are formed in excess and the steady-state between formation and elimination of ROS is disturbed, oxidative stress occurs.[4] During oxidative stress ROS cause damages to cell macromolecules meaning lipids, proteins and DNA and thus play an important role in aging and pathology

of different diseases (cardiovascular and neurodegenerative diseases, malignant tumors, osteoporosis, diabetes and others). Although traditionally ROS have been depicted as damaging to cells, evidence from recent years indicates that ROS are also essential components of normal cellular processes and may be indispensable to survival.

In this mini review we will mainly focus on the role of lipid peroxidation and its by-products in age-associated diseases.

## LIPID PEROXIDATION AND AGING-CONTRIBUTORS TO AGE-ASSOCIATED DISEASES

Aging is a genetic as well as epigenetic (patho) physiological process associated with morphological and functional changes in cellular and extracellular components aggravated by injury throughout life and resulting in a progressive imbalance of the control regulatory systems of the organism, including the hormonal, autocrine, neuroendocrine, and immune homeostatic mechanisms.[5] In general, aging is characteristically described as a time-dependent functional decline, leading to the incapacity of cells to withstand external and internal challenges, i.e. stress. According to this, aging is a consequence of two important biological processes: the loss of cellular/organic functionality and their loss of resistance or adaptability to stress. As mentioned before, aging is associated with a progressing imbalance between ROS formation and its degradation by antioxidative capacities, which includes the enzymatic scavengers superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and non-enzymatic scavengers of which the most important are some vitamins and glutathione (GSH). Biomolecular damage from ROS may be similar in all types of tissues but manifests in very different diseases depending on the proliferating and functional capacities of cells. Limited proliferation (cell division) may reduce risk of DNA damage but increases susceptibility of dysfunction to the damage of the proteins and membranous structures. On the other hand, frequent cell divisions may protect from the consequences of accumulated cellular damage on tissue function but increase susceptibility for DNA damage and malignant transformation.

Lipid peroxidation is an autocatalytic and degenerative process affecting cell membranes and other lipid-containing structures and is therefore associated with numerous pathological implications.[6] It is initiated by ROS generated under conditions of oxidative stress and ends in the formation of reactive aldehydes which are more stable than ROS, so they can diffuse from their site of origin and affect targets distant from the initial free radical attack. Increased lipid peroxidation has been implied with varying extents as causative cofactor of various common age-associated diseases, such as adult onset of diabetes mellitus, atherosclerosis, some types of cancer and some forms of (neuro) degenerative disorders. Still, major question requires answer in all of these diseases: does lipid peroxidation contribute to disease initiation and progression or is a consequence of these diseases?

One of the major toxic products generated during lipid peroxidation, considered as "second messenger of free radicals", is the α, β-unsaturated aldehyde 4-hydroxynonenal (HNE), which is derived from ω-6 polyunsaturated fatty acids such as arachidonic acid and linoleic acid.[6,7] HNE shows a variety of cytotoxic effects such as the inhibition of DNA, RNA and protein synthesis, cell cycle arrest, mitochondrial dysfunction, and thus plays an important role in pathology of various diseases. Intracellular HNE reacts rapidly with thiol groups of GSH and cysteine and with lysine and histidine residues of proteins.[8,9] Increased concentrations of HNE -modified proteins have been detected in different age-associated disorders, in particular in neurodegenerative disorders Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS),[10] atherosclerosis, cancer, diabetes, autoimmune diseases (rheumatoid arthritis), bone diseases (osteoarthritis, osteoporosis). However, HNE may act as a signaling molecule in pathological processes as well as under physiological conditions and is therefore considered also major "bioactive marker of pathophysiological processes" associated to lipid peroxidation.[11,12] As low levels of lipid peroxidation exist in normal tissues, this alde-

hyde displays signaling activities in normal cells. Among them, it is to consider the stimulation of neutrophil chemotaxis, activation of plasma membrane adenylate kinase, activation of membrane phospholipase C, inhibition of the oncogene c-myc expression, activation of the c-jun/jun kinases/AP-1 pathway, the effects on the cyclins and the activity of transcription factors.[4,12] Thus, HNE can induce proliferation, differentiation and apoptosis affecting genome function and interacting with other growth regulating factors, in particular cytokines.[13-16]

Taking into consideration all mentioned above, and keeping in mind the essential features of age-associated diseases pathology we can discuss whether lipid peroxidation and aging are cause or consequence of these diseases.

It is inevitable that metabolic disorders cause disruption in homeostasis and induce oxidative stress, consequently playing important role in pathology of certain age-associated diseases (i.e. neurodegenerative diseases, atherosclerosis, cancer, etc.) hence leading to accelerated aging. For instance in neurodegenerative diseases (AD, PD, ALS), the effects of oxidative stress on ''post-mitotic cells'', such as neurons may be cumulative, and cause peroxidation of membrane lipids or circulating lipoprotein molecules with consequential accumulation of highly reactive aldehydes. These by-products of lipid peroxidation induce accumulation of protein oxidized products like lipofuscin, and the HNE-protein adducts which could not be degraded by proteosome.[17,18] Therefore lipid peroxidation could be considered as predominant cause of these disorders though it is certain that the causes are multifactorial.[10]

On the other hand incidence of certain diseases (bone diseases, autoimmune diseases, skin deteriorations) increases with aging thus considering oxidative stress as a consequence. Although by-products of lipid peroxidation are present in these disorders it could be assumed that their presence is more due to aging (Figure 1, Table 1). Finally, persistent, but moderate oxidative stress could enhance antioxidant capacities and consequently reduce the risk of harmful effects of severe oxidative stress,

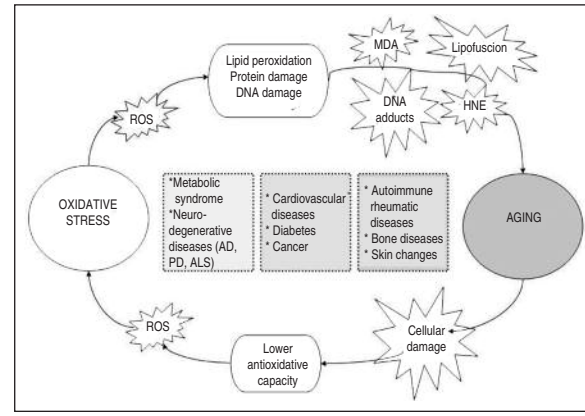


**FIGURE 1:** Role of oxidative stress and aging in initiation of age-associated diseases. Diseases in box nearer to oxidative stress or aging are more likely caused by these processes, while diseases placed in the middle could develop as a result of either of them.

including development of age associated diseases.[19]

Due to the regulatory effects of HNE, it is likely to assume that this physiologically present product of lipid peroxidation plays also a role in these beneficial consequences of oxidative stress, which need to be further clarified.

## CONCLUSIONS

Oxidative stress and lipid peroxidation should not only be considered as generators of biomolecular damage, and thus important contributors to aging as well as causative factors of diseases, but should also be recognized as significant mediators of normal physiological functions. Therefore we suggest considering three aspects of oxidative stress upon aging and prevalence of age-associated diseases.

1. Mild oxidative stress is a daily occurrence and can help maintain homeostasis. Due to continuous small doses of controlled oxidative stress (exercise) organism enhances its antioxidative capacity and thus can withstand increased levels of oxidative stress that results in lifespan prolongation and aging delay.

2. Since oxidative stress is important but not the only cause of aging it is likely that formerly bearable oxidative stress could become excessive during aging and thus favor genesis of certain diseases

**TABLE 1:** Arguments in favor of the presence of oxidative stress as a cause or as a consequence of aging in pathology of some age-associated diseases. Similar arguments could be used for various other diseases based on oxidative stress and lipid peroxidation.

| | Arguments in favor of disease as a consequence of | |
|---|---|---|
| **Disease** | **Oxidative Stress** | **Aging** |
| Cardiovascular disease | ROS oxidize low density lipoproteins (LDL) which are taken up by macrophages and from foam cells and plaques in the cardiovascular wall HNE is generated during peroxidation of LDL and modifies Apob protein. | Myocardium accumulates lipofuscin; mitochondria become samaller and numerous; arteries accumulate collagen, due to decrased elasticity they become rigid and veins curved. |
| Diabetes/metabolic syndrome | Oxidants inhibit glucose metabolism in the glycolytic pathway and at the level of oxidative phosphorylation, thereby causing a sugar overload in the blood which on the other hand causes auto oxidation of glucose and glycation of proteins. | Impairment of pancreatic beta cells causes decrease in insulin production, and insulin resistance increases due to accumulation fat and decreased tissue sensitivity to insulin. |
| Cancer | ROS attack biomolecules and cause structural damage to DNA. These changes manifest as point mutations and chromosomal alterations in cancer-related genes. Rapidly dividing cells will cause accumulation of damage and lead to transformation into malignacy. | Longer exposure to carcinogens (pollution, radiation, tobacco, sun, alcohol...), increase epigenetic gene silencing, telomere dysfunction, less effective DNA, repair system that allows mutations to accumulate more rapidly |

ROS: Reactive oxygen species.

like cancer, cardiovascular diseases, diabetes and neurodegenerative diseases. Occurrence of such diseases contributes to homeostasis disruption, organism exhaustion and therewith anticipates aging.

3. People who show aging acceleration and are more susceptible to occurrence of age-associated diseases either due to genetic (such as Down's syndrome) and/or due to unfavorable epigenetic factors as in case of stressful professions like managers, pilots, truck drivers, computer game programmers, etc.

Therefore, we could consider lipid peroxidation associated disorders and aging as mutually dependent processes, which could be attenuated by mild and well tolerated oxidative stress acting as a possible defense against initiation and progression of age-associated diseases.

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