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# Lipid Peroxidation: Aging Kidney

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## **Abstract**

Kidney is one of the tissues affected by age that involves cellular and structural changes inside the kidney and notably implicates with comorbidity, related to cardiovascular disease aging. Aging kidney causes the elderly susceptible to clinical deterioration from ordinary stimulation that younger individual can compensate, including acute renal injury, volume depletion or overload, sodium and potassium level disorders, and toxic reaction against kidney excreted drugs. As one of the organs with the fastest aging rate, kidney shows several age-related decline in both structural and functional with 30% of the glomerulus are damaged and represent diffuse glomerular sclerosis by age 75 and explain why the prevalence of chronic kidney disease (CKD) and end-stage renal disease are very common in the elderly. The cross-sectional population-based study by The National Health and Nutrition Examination Survey supports the theory of age-related decline in kidney function, although some other subjects did not have an absolute decline in kidney function. The underlying molecular mechanisms could be the target of future therapeutic strategies. Aging is a natural biological process characterized by a gradual decline in cellular function as well as progressive structural change of organ systems. In aging kidney, there are interactions of genetic factors, environmental changes, and cellular dysfunction that lead to the typical structural and functional changes. One of the most popular theory of aging is the theory of free radicals or oxidative stress based on the fact that cells are under chronic oxidative stress due to an imbalance between pro oxidants and antioxidants. Reactive oxygen species are oxygen-derived oxidizing compounds that are highly reactive, consisting of free radicals and non-radicals. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) refer to both reactive radicals and non-radical derivatives of oxygen and nitrogen. Reactive oxygen and nitrogen species (RONS) are produced by all aerobic cells and play an important role in aging as well as age-related diseases. Lipid peroxidation is a process of oxidative degradation of lipids that process by which free radicals bind to lipid electrons in the cell membrane resulting in direct cell damage. Lipid peroxidation can cause cellular damage in several ways such as impairing the integrity of the plasma membrane and subcellular organelles by peroxidation, “chain reaction” of ROS production, and activation of phospholipase A2 (PLA2) caused by lipid peroxidation. Fatty acids and other PLA2 metabolites (such as lysophospholipids) are known to damage cell membranes. In the development of kidney damage, the process of lipid peroxidation plays an important role. This is presumably due to the large number of long-chain polyunsaturated fatty acids (PUFAs) in the lipid composition of the kidneys and there are substantial evidence to suggest that ROS is involved in the ischemic, toxic, and immunologically mediated pathogenesis of renal injury, but the cellular mechanisms that result in cell injury and death are still being studied.

**Keywords:** oxidative stress, aging, kidney

## 1. Introduction

Kidney is one of the tissues affected by age. Aging involves cellular and structural changes inside the kidney and notably implicates with comorbidity, related to cardiovascular disease aging [1, 2]. The Centers for Disease Control and Prevention estimated that 72 million people in the United States (20% of population) will be 65 years old or more at 2030. Eurostat estimated, around 28% Europeans will be 65 years old at 2060. The increasing number of older adults will be predicted to increase aging related kidney disorders as well [3].

Aging kidney causes the elderly susceptible to clinical deterioration from ordinary stimulation that younger individual can compensate, including acute renal injury, volume depletion or overload, sodium and potassium level disorders, and toxic reaction against kidney excreted drugs [4]. Deficiency of kidney function is associated with death in all populations [2]. Several studies have shown that the decrease of function related to be structural (glomerulosclerosis, tubular atrophy and interstitial fibrosis) and functional (reduced glomerular filtration rate, proteinuria, decreased ability to concentrate or dilute urine, electrolyte imbalance and ion transport disorders, changes in hormonal function, reduced drug excretion) [1, 5].

As one of the organs with the fastest aging rate, kidney shows several age-related decline in both structural and functional. The renal parenchyma decreases about 1%, and creatinine clearance or GFR decrease is about 1.0 mL/minute per 1.73 m<sup>2</sup> per year in elderly subjects [6]. In normal aging kidneys, 30% of the glomerulus are damaged and represent diffuse glomerular sclerosis by age 75. Meanwhile the remaining glomerulus denote impaired filtration ability [2]. This could explain why the prevalence of chronic kidney disease (CKD) and end-stage renal disease are very common in the elderly [6]. Chronic kidney disease is a major growing health and economic burden. About 8–13% of the world's population suffers from CKD [7].

## 2. Age-related kidney changes

Age-related loss of kidney function has been recognized for decades. The cross-sectional population-based study by The National Health and Nutrition Examination Survey supports the theory of age-related decline in kidney function, although some other subjects did not have an absolute decline in kidney function. Although the rate of this decline is low, the process may have negative effects on many organ systems and thus reduce overall health and physical function in the elderly individual [6]. Epidemiological, clinical, and molecular evidence suggest that aging is a major contributor to the increased incidence of acute kidney injury and CKD. Renal function recovery after an episode of acute kidney injury is significantly worse in elderly patients. Reduction of regenerative potential, which is a feature of the aging process, may be caused by aging cells [8].

With increasing age, many individuals show progressive reductions in glomerular filtration rate (GFR), renal blood flow (RBF), and loss of nephron function with wide variability between individuals [9]. The aging kidney undergoes complex changes that affect the pathology of the kidney. The underlying molecular mechanisms could be the target of future therapeutic strategies [8].

The accumulation of old cells explains the ineffectiveness of cell repair and the loss of functional ability wherein studies have shown that the removal of old cells results in delayed kidney aging. Other potential mechanisms are autophagic changes responding to renal stress and the inflammatory response [8].

### 3. Kidney aging and oxidative stress

Aging is a natural biological process, progressive and inevitable characterized by a gradual decline in cellular function as well as progressive structural change of organ systems. This reduction means a reduced capacity to maintain homeostatic control over essential functions and ultimately results in the death of the organism [5, 10]. These anatomical and physiological changes are called senescence, a term that describes changes more related to age than changes caused by disease [11].

The aging mechanism does not stand alone but involves the interaction of several factors. These factors were put forward by Fontana and Klein: (1) Oxidative stress will damage protein and DNA, this condition is also followed by a decrease in the ability to repair DNA, and an imbalance in the mitochondrial and nucleus genome; (2) The existence of chronic inflammation which increases with age; (3) Changes in fatty acid metabolism, which acid is associated with insulin resistance. So that there is excess free fatty acids in plasma; (4) There is an interruption of normal cell physiology due to excessive excess of metabolic and product such as Advanced glycolysis end products (AGE), amyloid, and other proteins; (5) the sympathetic nervous system and the activation of angiotensin system and changes in the neuro-endocrine system; (6) post-mitotic cell loss, resulting in a decrease in the number of neurons and muscle cells and damage to cell structure and function in all tissues and organs [12].

The kidneys have higher activity (highly energetic) than other organs, thus they produce a lot of free radicals as intermediate substances (as free radical stores) which cause oxidative stress which results in impaired signal delivery, increased apoptosis, decreased ability to regenerate cells, and fibrosis in the kidneys. This characteristics make kidney one of the organs that ages more rapidly than the other organs [13].

In aging kidney, there are interactions of genetic factors, environmental changes, and cellular dysfunction that lead to the typical structural and functional changes. The exact biological and cellular mechanisms responsible for aging are not yet known. One of the most popular theories of aging is the theory of free radicals or oxidative stress. This theory is based on the fact that cells are under chronic oxidative stress due to an imbalance between pro oxidants and antioxidants [14, 15].

This theory states that aging is caused by accumulated oxidative damage. As organisms getting older, they produce more free radicals, some of which are not completely neutralized by the endogenous antioxidant defense mechanisms. These free radicals then react with biomolecules and cause the accumulation of toxic oxidative products that lead to oxidative stress and accumulation of toxic oxidative products [10].

The kidneys depend on aerobic metabolism and oxidative phosphorylation for the production of the energy required for tubular reabsorption [16]. Due to their high metabolism, the kidneys are very susceptible to oxidative damage, and several trials have shown that oxidative stress can cause or accelerate the progression of kidney disease and its complications [17]. Most of the age-dependent renal changes such as excessive fibrosis, general lack of regenerative ability, and increased apoptosis in cells that determine healthy kidney function are often associated with excess OS [18].

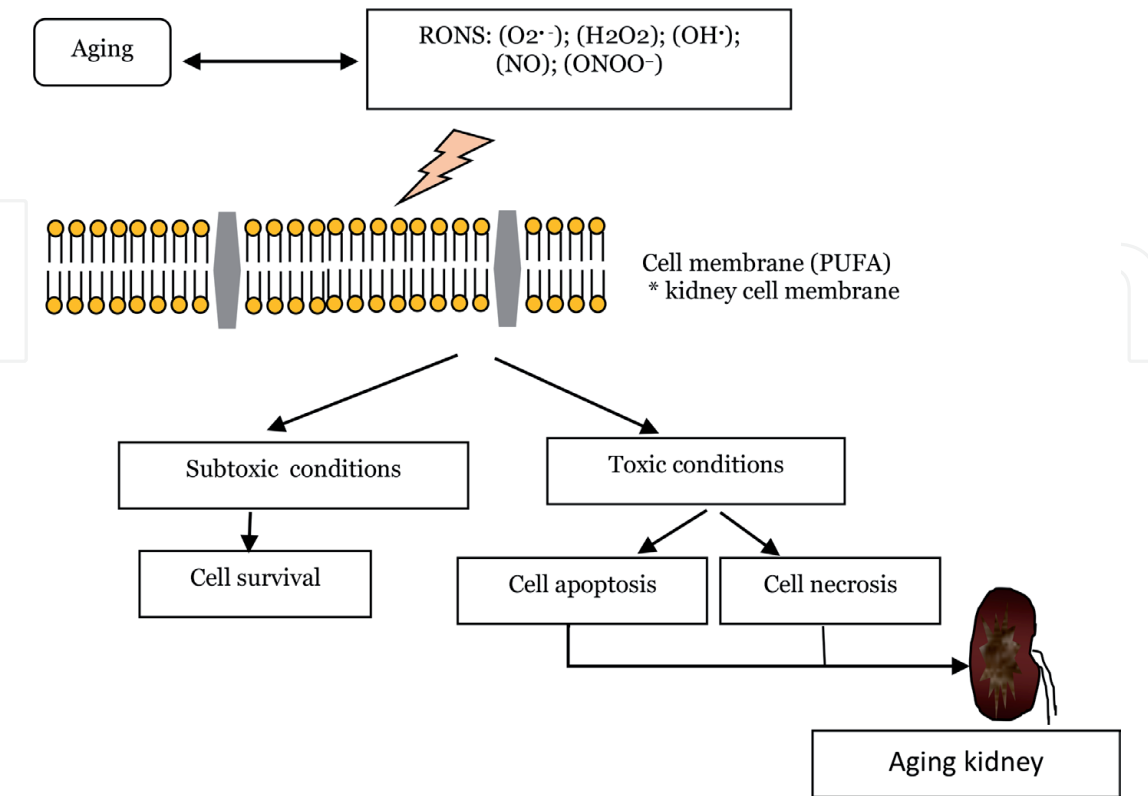
The mechanism of free radicals damaging cells can be in several ways: (1) free radicals will damage the double layer lipid membrane causing disruption of the fluidity and permeability properties of the membrane. (2) Free radicals enhance protein cross-linking processes, especially those mediated by sulfhydryl groups, resulting in degradation and loss of cell activity. (3) DNA damage induced by free

radicals causes the breakdown of DNA strands. (4) Impaired function of cellular receptors, neurotransmitters and hormonal responses due to oxidative damage to carbohydrates [17].

Research shows that in the aging process of organisms, excessive oxidative stress can activate many pro inflammatory pathways, including the NF- $\kappa$ B signaling pathway. Oxidative stress also induces ongoing regulation (chronic) of pro inflammatory mediators (such as TNF- $\alpha$ , IL1- $\beta$ , IL-6, COX-2, iNOS) which lead to tissue and organ aging [19]. Besides, oxidative stress is also involved in various disease processes and degenerative syndromes. In mild oxidative stress due to normal metabolism results; The resulting biomolecular damage cannot be completely repaired or eliminated by cell degradation systems, such as lysosomes, proteasomes, and cytosol and mitochondrial proteases [12].

In oxidative stress, oxygen-free radicals are formed excessively as well as  $H_2O_2$ , so that the body's protection system such as catalase and glutathione peroxidase enzymes can no longer neutralize all oxygen free radicals that are formed. Furthermore, if  $H_2O_2$  reacts with  $Fe^{2+}$  and  $Cu^{2+}$ , hydroxyl free radicals are formed through the Fenton and Haber-Weiss reaction. The hydroxyl radical is a very reactive species.

Reactive oxygen species and reactive nitrogen species can attack all types of biomolecules, especially unsaturated fatty acids which are important components of phospholipids making up cell membranes. This accumulation of oxidative damage is considered to be an important mechanism underlying aging and an increase in age-related pathology, as well as a progressive decrease in the functional efficiency of various cellular processes [14, 15]. Among the ROS, the most widely known, are superoxide ion ( $O_2^{\cdot-}$ ), hydrogen peroxide ( $H_2O_2$ ), and peroxy radicals ( $OH^{\cdot}$ ), while RNS is nitric oxide (NO) and peroxy nitrite ( $ONOO^-$ ) (**Figure 1**) [18]. At the molecular level, increased oxidative damage and its products have been reported. This contributes to a chronic inflammatory response with the accumulation of macrophages and lymphocytes in the interstitium [1].



**Figure 1.** Schematic mechanism of cell damage according to the theory of free radical aging. In this case the kidney.



In certain conditions that are triggered by oxidative stress, there is an insufficiency of endogenous antioxidants, both enzymatic and non enzymatic. Enzymatic antioxidants include glutathione peroxidase, catalase, and superoxide dismutase. Non enzymatic antioxidants include vitamin E, vitamin C, thiol antioxidants (glutathione, thioredoxin, and lipoic acid), melatonin, carotenoids, natural flavonoids, and others [7, 20]. Studies on old mice kidneys support the theory that there is a decreased antioxidant capacity and decreased levels of Cu/Zn-SOD, catalase, and GSH reductase.

Several processes can suppress oxidative stress: (1) reduce radiation and pollutant that affect the environment; (2) enhance antioxidant both endogen and exogen to neutralize ROS before it oxidizes cells; (3) suppress oxidative stress formation through stabilization of production and efficiency of energy in mitochondria [12].

#### 4. The source of ROS formation

Reactive oxygen species are oxygen-derived oxidizing compounds that are highly reactive, consisting of free radicals and non-radicals. Apart from oxygen derivatives, free radicals also come from nitrogen derivatives. Free radicals are atoms or molecules with unpaired electron, which are very unstable and very reactive. Therefore, they try to pair up with the free electrons around them, so that they will form other free radicals or paired electrons, where their radical characteristics may be lost. If a new free radical is formed, it is also unstable and react with other molecules to produce other free radicals or non-radical molecules due to the electron pair of the new formed molecule. Thus, a free radical chain reaction will form excessive free radicals.

Free radicals include superoxide anion ( $O_2^-$ ), Hydroxyl radicals ( $OH^\cdot$ ), hydroperoxyl ( $HO_2$ ) Peroxyl radicals ( $RO_2^\cdot$ ), alkoxyl ( $RO^\cdot$ ), carbonate ( $CO_3^\cdot$ ), nitric oxide ( $NO^\cdot$ ), nitrogen dioxide ( $NO_2^\cdot$ ), peroxy nitrite ( $ONOO^\cdot$ ), nitroxyl ion, purine radical. Meanwhile, non-radicals are hydrogen peroxide ( $H_2O_2$ ), organic peroxides ( $ROOH$ ), ozone, oxygen siglet, and lipidperosides.

Free radicals are formed in cells through oxidation and reduction of one electron. If the formed free radicals are the oxygen's derivative, they are called reactive oxygen species (ROS). Reactive nitrogen species (RNS) are those derived from nitrogen. All of aerobic cells will produce reactive oxygen and nitrogen species (RONS) which have critical role in cell's aging and age-related diseases. The formation of RONS is not only limited to its deleterious effects but also plays a role in energy extraction from organic molecules, immune defense, and signaling processes [18, 20].

Sources of RONS can be endogenous and exogenous. Endogenous sources of RONS are generated by several major enzymatic processes such as cellular respiration (by the mitochondrial electron transport chain) or the activity of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex [7, 20]. Approximately 1–4% of the oxygen metabolized by mitochondria is converted to superoxide ions which in turn produce free radicals capable of damaging structural proteins and DNA [12]. Exogenous generated RONS are induced by external factors, such as chemical pollutants, environmental pollutants, such as cigarette smoke, some drugs, exposure to UV rays, alcohol, ionizing radiation, pesticides, ozone [12, 20]. X-rays and ultraviolet rays can break down water to form radicals ( $OH^\cdot$ ). Metal ions such as  $Fe^{2+}$ ,  $Ca^{2+}$ ,  $Cu^+$ , can also react with oxygen or hydrogen peroxide to produce OH radicals.

Among the ROS, the most widely known are superoxide ions ( $O_2^{\bullet-}$ ), hydrogen peroxide ( $H_2O_2$ ), and peroxy radicals ( $OH^{\bullet}$ ), while RNS is nitric oxide (NO) and peroxy nitrite ( $ONOO^-$ ) [18]. In general, free radicals are needed for the continuity of physiological processes, especially for electron transport, cell development, as well as helping leukocytes in destroying germs in the immune system. When free radical products are balanced with the antioxidant capacity, it directs cells into growth, signaling and survival.

If these free radical products exceed the antioxidant capacity, cells will lead to oxidative stress, apoptosis and necrosis [18]. Mitochondria play an important role in the aging process because these organelles are the main source of free radical production as a side effect of energy formation. Mitochondrial dysfunction has long been considered a major contributor to aging and age-related diseases. In young mitochondria, this condition can be overcome by the presence of antioxidants in the body. However, the old mitochondria do not produce enough of the antioxidants needed to neutralize the free radicals that are formed, so there is an imbalance between the production of free radicals and antioxidants. Apart from that, mitochondria also play an important role in amino acid and lipid metabolism, calcium homeostasis, apoptosis regulation, cell cycle regulation, and thermogenesis [15, 21]. Renal fibrosis results from loss of ATP production due to mitochondrial dysfunction, which is associated with increased free radical formation and oxidative stress. Thus, oxidative stress, which involves various reactive oxygen and nitrogen species, has an important role in the pathophysiology of CKD [16].

Dysfunction of the mitochondrial electron-transport system leads to increased production of ROS, which results in mtDNA damage followed by mutations that lead to impaired mitochondrial protein function and a further increase in RONS production [21]. Electron leakage causes the reduction of one oxygen electron to form superoxide anions which are the precursors of most ROS and mediators in oxidative chain reactions. The superoxide anion then undergoes dismutation which is catalyzed by superoxide dismutase to produce durable hydrogen peroxide and a permanent membrane. This molecule can be reduced entirely or partially to water or hydroxyl radicals. Under normal conditions, ROS is maintained at a physiological level by several systems of endogenous antioxidant enzymes, such as SOD, catalase, glutathione peroxidase and glutathione reductase [17].

## **5. Lipid peroxidation**

Oxidative stress causes tissue damage including the kidneys by a variety of different mechanisms, specifically damaging cell membranes, DNA damage, and protein modification. The term lipid peroxidation is a process of oxidative degradation of lipids. Lipid peroxidation is a process by which free radicals bind to lipid electrons in the cell membrane resulting in direct cell damage. The kidneys are highly susceptible to damage caused by ROS, possibly due to the large number of long-chain polyunsaturated fatty acids (PUFAs) in the lipid composition of the kidneys [18]. Allylic hydrogen in PUFA is very sensitive to free radical attack [14].

In response to membrane lipid peroxidation, depending on the specific cellular metabolic state and repair capacity, cells may increase cell survival or cause cell death. In conditions where the level of lipid peroxidation is physiological or low (called the subtoxic state), cells stimulate their maintenance and survival through constitutive antioxidant defense systems or activation of signaling pathways that regulates antioxidant proteins resulting in adaptive stress responses. Conversely, under moderate or high levels of lipid peroxidation (toxic conditions), the rate of oxidative damage exceeds the repair capacity. This causes programmed cell death,

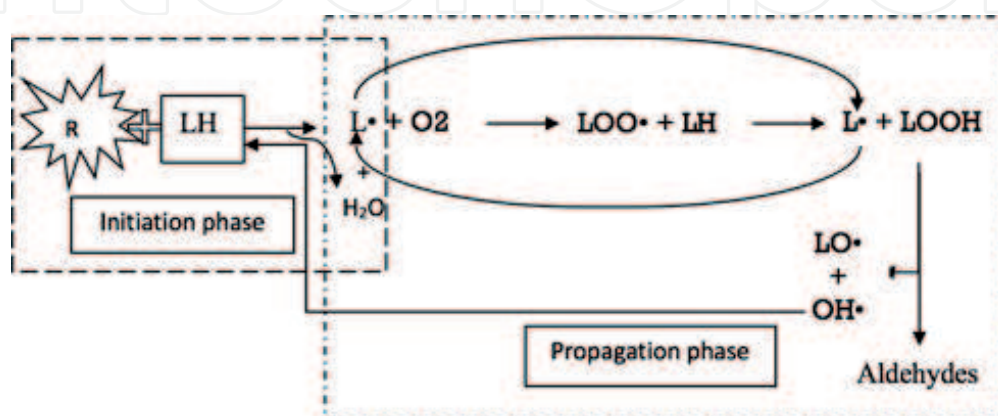
apoptosis or necrosis; both processes eventually cause molecular cell damage which can facilitate the development of various pathological conditions, and also accelerate aging [22].

Lipid peroxidation plays an important role physically because it decreases membrane fluidity, thereby facilitating the exchange of phospholipids between two monolayers, and increases the leakage of the bilayer membrane to substances that do not normally cross the membrane other than through certain channels [14]. Lipid peroxidation is followed by oxygen release, which is reduced into water via the mitochondrial respiratory chain. At the same time, lipids can be oxidized by efficient ROS initiators, particularly hydroxyl radicals and dihydroxyl radicals ( $\text{HO}_2^\bullet$ ), forming water and lipid radicals. This process leads to initiation of lipid peroxidation reactions, which are constantly occurring in the cell [23].

Lipid peroxidation is an autocatalytic radical process which consists of three stages; the first is initiation, followed by propagation, and the last is the cessation of peroxidation which is the result of lipid radical interactions and/or the formation of non-radical species due to the action of peroxy radicals. Lipid peroxidation is primarily initiated by hydroxyl radicals, which are generated through reactions catalyzed by transition metals, such as the Fenton reaction [24].

At the initiation step of lipid peroxidation, prooxidants such as hydroxyl radicals ( $\text{OH}^\bullet$ ) abstract allylic hydrogen to form carbon-centered lipid radicals ( $\text{L}^\bullet$ ). In the propagation phase, the lipid radical ( $\text{L}^\bullet$ ) rapidly reacts with oxygen to form peroxy lipid radical ( $\text{LOO}^\bullet$ ). Lipid peroxy radicals are unstable molecules and can combine with other fatty acids ( $\text{LH}$ ) nearby to form different lipid hydroperoxides ( $\text{LOOH}$ ) and lipid radicals. Lipid peroxy radicals can also react with themselves. The lipid hydroperoxides can then be broken down into alkoxy lipid radicals ( $\text{LO}^\bullet$ ) and hydroxyl radicals ( $\text{OH}^\bullet$ ). The lipid radicals formed in the previous stage can react with oxygen to produce other lipid peroxy radicals, and so on. So, this process is called the “lipid peroxidation chain reaction” (**Figure 2**) [22–24].

Once formed,  $\text{LOOH}$  can undergo reductive degradation which reduces or increases the cytotoxic potential, depending on the underlying conditions. In addition,  $\text{LOOH}$  or other intermediate peroxidation products can trigger signal transduction pathways requiring greater cytoprotection shelter (eg. upregulation of detoxification enzymes) or planned termination (apoptotic death) [25]. Lipid hydroperoxides are fairly stable compounds, but their decomposition can be catalyzed by transition metals and metal complexes, giving rise to new radicals capable of stimulating further lipid peroxidation or the formation of oxidation end products with various toxicities, such as malondialdehyde (MDA), hydroxynonenal



**Figure 2.** Schematic reaction of the lipid peroxidation chain.  $\text{LH}$ —lipid molecules,  $\text{L}^\bullet$ —lipid radicals,  $\text{LOO}^\bullet$ —lipid peroxy radical,  $\text{LOOH}$ —lipid hydroperoxide,  $\text{LO}^\bullet$ —lipid alkoxy radical,  $\text{OH}^\bullet$ —hydroxyl radical,  $\text{HO}_2^\bullet$ —Perhydroxyl radical. The stopping phase occurs until the substrate runs out or the process is stopped by antioxidants.



and hexanal. This reaction will continue until the substrate runs out, or the process is interrupted by antioxidants [24].

In the stopping phase, an antioxidant such as vitamin E donates a hydrogen atom to the  $\text{LOO}^\cdot$  species and forms the associated vitamin E radical which reacts with other non-radical  $\text{LOO}^\cdot$  forming products. After lipid peroxidation has started, a multiplication chain reaction will continue until a stopping product is produced [22, 23].

Lipid peroxidation produces a wide variety of oxidation products. The primary product of lipid peroxidation is lipid hydroperoxide ( $\text{LOOH}$ ). Secondary products of lipid peroxidation include malondialdehyde (MDA), propanal, hexanal and 4-hydroxynonenal (4-HNE). Among these secondary products, MDA appears to be the most mutagenic lipid peroxidation product, whereas 4-HNE is the most toxic [22]. Peroxidation products are involved in many cellular processes including cell metabolism, signaling, and cell survival. Lipid molecules, particularly PUFAs and cholesterol, undergo variable oxidation rate initiated by RONS [26].

## **6. Lipid peroxidation and its effects on the kidneys**

Aging is associated with increased oxidative stress. Most of the changes in the kidneys are age dependent, such as excessive fibrosis, lack of regenerative ability in general, and increased apoptosis. At the molecular level there is an increase in mutations in both nuclear and mitochondrial DNA (mtDNA), increased lipofuscin, AGEs, oxidative stress and apoptosis. Proximal tubular cells contain a large number of mitochondria and are most dependent on oxidative phosphorylation and are most susceptible to apoptosis, oxidant-induced mutations. Recent studies have shown that the anti-aging gene, *klotho*, is an important factor in kidney aging and kidney damage due to oxidative stress [18].

Lipid peroxidation can cause cellular damage in several ways. First, the integrity of the plasma membrane and subcellular organelles are impaired by peroxidation. Second, the interaction of ROS with PUFAs leads to the formation of additional radicals (hydroperoxide and hydroperoxide metabolites) which result in a “chain reaction” of ROS production. This process increases the production of ROS which can cause cell damage by interacting with cellular proteins and DNA. Finally, lipid peroxidation causes activation of phospholipase A2 (PLA2). Fatty acids and other PLA2 metabolites (such as lysophospholipids) are known to damage cell membranes. So PLA2-induced free fatty acid release can cause additive injury to the cell membrane [27].

In the development of kidney damage, the process of lipid peroxidation plays an important role [28]. The kidneys are organs that are highly susceptible to damage caused by ROS. This is presumably due to the large number of long-chain polyunsaturated fatty acids (PUFAs) in the lipid composition of the kidneys [18]. There is substantial evidence to suggest that ROS is involved in the ischemic, toxic, and immunologically mediated pathogenesis of renal injury [29]. Experimentally it has been shown that ROS plays a role in the pathogenesis of kidney disease, but the cellular mechanisms that result in cell injury and death are still being studied [27].

In general, human and animal studies suggest that lipid oxidation plays an important role in predicting the development of cardiovascular and renal disease and the response to therapy. In kidney disease, the use of biomarkers such as malondialdehyde (MDA), isoprostanes (IsoPs) or isolevuglandins (IsoLGs) has been reported. Malondialdehyde can interact with proteins and can potentially cause atherogenicity [7].

ROS causes lipid peroxidation in cell membranes and organelles, thereby impairing structural integrity and capacity for cell transport and energy production,

particularly in the proximal tubular segment. In addition, lipid peroxidation co-mediate decreased glomerular blood flow and glomerular filtration through release of vasoconstrictive bioactive lipids (prostaglandins, thromboxanes, and platelet activating factors) and, possibly, nitric oxide relaxation inactivation [29].

Li et al's study of 2,169 adult patients stated that oxidative stress can be demonstrated by plasma MDA levels associated with the prevalence of mild acute renal insufficiency and/or CKD. Although MDA increases the load on the kidneys and/or causes oxidative stress cycle in the body, high levels of MDA in plasma may be associated with age-related decline in kidney function as well [6].

Gomes et al. examined renal oxidative stress status in old Wistar Kyoto (WKY) mice. This research was conducted by measuring H<sub>2</sub>O<sub>2</sub> levels in the kidneys. In this study, it was found that the renal and medullary cortical H<sub>2</sub>O<sub>2</sub> production increased sharply in old WKY. This suggests that the dramatic increase in the rate of H<sub>2</sub>O<sub>2</sub> production in the old WKY kidney is indicative of a significant increase in oxidative stress in this tissue. Moreover, increased renal ROS production and lipid-related oxidative damage may play a role in the pathogenesis of kidney disease. Overall, these data suggest that elderly WKY exhibits the first signs of renal oxidative damage [5].

Lim et al's study on old C57/BL6 mice showed that aging kidneys exhibited increased levels of reactive oxygen species and thiobarbiturate acid reactive substances, which are associated with oxidative lipid damage. In addition, other markers of oxidative stress and lipid peroxidation, such as isoprostane, AGE, and elevated heme oxygenase, were also found in old mice. This research also shows that Sirtuin 1 and Klotho also decrease with aging [30].

Antioxidant enzymes are able to remove reactive oxygen species and lipid peroxidation products. In aging, physiological functions change due to a decrease in endogenous antioxidants, such as SOD, CAT, and GSH-Px. In contrast MDA, a good indicator of lipid peroxidation showed an increase. Chen et al. in their study of old mice showed that the activity of SOD, CAT and GSH-Px in the liver and kidneys decreased compared to the group of young mice. In addition, MDA levels in the liver and kidneys of old rats were increased compared to the group of young mice [31].

Besides the endogenous antioxidants above, there is also a role for enzymes involved in oxidative stress response, aging and various metabolic regulation in the body, namely Sirtuin1. This enzyme is known as the master regulator. Starting with the discovery of the silent information regulator 2 (Sir2) gene in yeast in 1986. Where the long-lived yeast has an overexpression of this gene, while in the shorter-lived yeast it is found to have low expression. Since then Sir2 is believed to be a gene that plays a role in longer survival (longevity) [32, 33]. Homologous Sir2 gene in mammals, is sirtuin (SIRT).

Sirtuin is a class III histone deacetylase protein group that has deacetylation activity against histones and non-histones that do not contain nicotinamide adenine dinucleotide (NAD) deacetylase and/or adenosine diphosphate (ADP) ribosyltransferase. This enzyme works with the help of the coenzyme NAD to carry out its function [34]. Sirtuin 1 (SIRT1) is considered to be most homologous to yeast sir2. In the study of young mice, Sirtuin1 is expressed by various cells in organs such as kidneys, liver, lymph, skin, but mostly in the kidneys, especially the medulla [35–38].

Sirtuin 1 not only has deacetylation activity against histones but also on many transcription factors and cofactors, such as p53, FOXO, peroxisome proliferator activated receptor  $\gamma$  (PPAR- $\gamma$ ), co-activator-1 $\alpha$  and NF- $\kappa$ B which play a role in crucial cellular activity including the response to stress, metabolism and longevity (cell senescence) [39, 40].

As a function of redox regulator, sirtuin detects surrounding imbalance through NAD levels, sirtuin 1 will deacetylate the substrate so that it will activate antioxidant genes such as SOD2 (superoxide dismutase 2), GPX1 (glutathione peroxidase 1) which can anticipate free radicals. Under conditions of oxidative stress, sirtuin can produce O-acetyl-ADP ribose (OAADPR) which can turn into ADP ribose, both of which have a protective effect against oxidative stress [41].

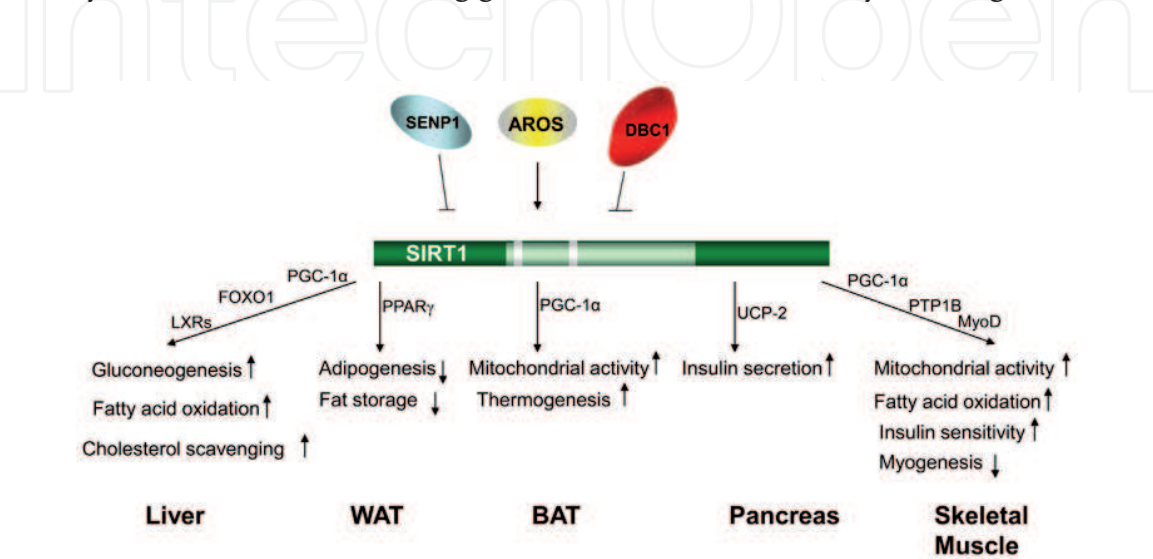
The role of sirtuin through the Forkhead box (FOXO) is to regulate apoptosis, lipid metabolism, cell proliferation, inflammation, autophagy and stress resistance. Where FOXO3 acetylation expresses apoptosis-related genes, such as: Bim, TRAIL and FasL [33]. Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a widespread transcription factor affecting inflammation, apoptosis, adhesion and the cell cycle through regulation of target genes. Sirtuin can inhibit the activity of NF- $\kappa$ B so that it can play a role in glucose control, AGEs, cytokines, growth factors, dan toll-like receptors [42].

Sirtuin 1 regulates lipid homeostasis by regulating the sterol regulatory element binding protein (SREBP), liver X receptor (LXR) and farnesoid x receptor (FXR). Sirtuin 1 directly deacetylates SREBP, inhibits SREBP target gene expression and reduces lipid and cholesterol levels [33, 34]. Tumor suppressor p53 is a transcription factor associated with oxidative stress responses. With the ability of SIRT 1 to deacetylate P53 it will reduce transcription activity.

Increased oxidative stress in the elderly will decrease SIRT1 levels, resulting in increased inflammation, increased apoptosis, decreased autophagy, decreased levels of endothelial nitric oxide synthase (eNOS), increased AT1R expression, reduced ability in redox reactions and lipid metabolism. The reduced expression of SIRT1 due to aging will make the kidneys prone to progressive structural and functional disorders (**Figure 3**) [12, 33, 43].

Kume et al. (2010) found the association between mitochondrial damage of proximal tubular cells in aging kidneys with reduced expression of sirtuin. In proximal tubular cells of old mice, autophagy responses to kidney hypoxia were decreased and caused dysfunction and fibrosis. Increasing sirtuin expression by caloric restriction helps improvement of aging kidneys [44]. The similar result was stated by He et al. (2010), who found sirtuin expression protected kidneys in oxidized state and provided anti apoptotic and anti fibrotic effects to kidneys [45].

Kidney function is determined by glomerular filtration rate. This filtration barrier consists of endothelial cells, glomerular basal membrane and podocytes. Podocyte is critical in maintaining glomerular filtration. Podocyte damage caused



**Figure 3.**  
*The role of SIRT1 in metabolic Homeostais [42].*

by oxidative stress leads to reduction of glomerular filtration rate. Sirtuin preserves homeostasis and protects podocytes from oxidation.

Transforming growth factor (TGF)- $\beta$  is a key cytokine that regulates apoptosis, cell cycle, differentiation and accumulation of extracellular matrix. Association between TGF- $\beta$ /Smad and kidney fibrosis occurrence has been proven in many studies. Sirtuin, which suppress expression of TGF- $\beta$ , is decreased in aging kidneys. This results in increased expression of TGF- $\beta$  thus also increases kidney fibrosis.

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