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Relationship between free radicals and risk of kidney diseases; the role of antioxidants and their reaction mechanisms

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Abstract

Free radicals are regularly formed in the human body and are often associated with tissue injury. They are harmful to the body and damage all components of cells, including proteins, DNA, and cell membranes. Antioxidants protect the body from damage caused by free radicals. The lack of balance in production of free radicals and the ability of the body to negate their dangerous effects through neutralization by antioxidants produce oxidative stress (OS). OS has an important role in the pathophysiology of several kidney diseases. There are many experimental evidences suggesting key role of OS and inflammation on renal failure. There are many reports which suggest that the use of antioxidants help in the disease prevention. Therefore, it is very important to understand the reaction mechanism of antioxidant with the free radicals. This review explains the relationship between free radicals and risk of kidney diseases, the role of antioxidants in the diseases prevention and reaction mechanisms of the antioxidants.

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Introduction

Free radicals are regularly formed in the human body and often associated with tissue injury. Antioxidants are free radical scavengers that react with the free radicals and delay the cellular damage. The lack of balance in production of free radicals and the ability of the body to negate their dangerous effects through neutralization by antioxidants produce oxidative stress (OS). OS has an important role in the pathophysiology of several kidney diseases. There are many experimental evidences suggesting a key role for OS and inflammation on renal failure (1,2). There are many reports which suggest that the use of antioxidants help in the disease prevention (3-5). Hence, it is very important to realize the reaction mechanism of antioxidant with the free radicals. To realize the mechanism of action of antioxidants, it is required to realize the production of free radicals and their harmful reactions. This review explains the generation of free radicals and the damages that free radicals may create and the reaction mechanisms of antioxidants. Also, the relation between OS and risk of kidney diseases and the role of antioxidants in prevention and treatment of these diseases are discussed.

Core tip

Antioxidants protect the body from damage caused by free radicals. The lack of balance in production of free radicals and the ability of the body to negate their dangerous effects through neutralization by antioxidants produce oxidative stress (OS). OS has an important role in the pathophysiology of several kidney diseases. There are many experimental evidences suggesting key role of OS and inflammation on renal failure. There are many reports which suggest that the use of antioxidants help in the disease prevention. Therefore, it is very important to understand the reaction mechanism of antioxidant with the free radicals. This review explains the relationship between free radicals and risk of kidney diseases, the role of antioxidants in the diseases prevention and reaction mechanisms of the antioxidants.

Materials and Methods

For this review, we used a variety of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and, or their equivalents; free radicals, reactive oxygen species,

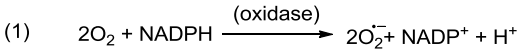
antioxidants, OS and renal disease.

Generation of free radicals in body

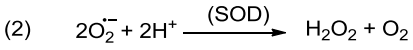
Free radicals are molecules with free unpaired electrons. They are very unstable and highly reactive. These compounds are regularly formed in the human body and are often associated with tissue injury. The majority of free radicals are oxygen radicals and other reactive oxygen species (ROS) that are listed in Table 1 (6).

ROS are produced in mitochondrial electron transport system, peroxisomal fatty acids, cytochrome P-450, and phagocytic cells. Drugs, illness, stress, pollution, cigarette smoke, and even exercise can increase free radical exposure. The sources of free radicals formation are showed in Table 2 (7).

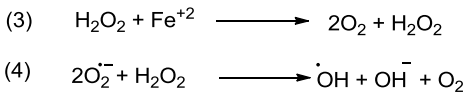
Superoxide is produced in mitochondrial electron transport chain by a variety of enzymatic processes such as the NAD(P)H oxidase (Eq. 1).



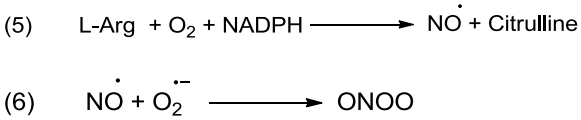
The $O_2^{\bullet-}$ is then rapidly converted into H_2O_2 (Eq. 2) by SOD.



•OH is also produced from $O_2^{\bullet-}$ and H_2O_2 via 'respiratory burst' by Fenton (Eq. 3) and / or Haber-Weiss reactions (Eq. 4) (8).



NO is generated from arginine by an enzymatic processes (Eq. 5). The NO• and $O_2^{\bullet-}$ react together to produce peroxynitrite (ONOO) (9).



Damaging reactions of free radicals in the body

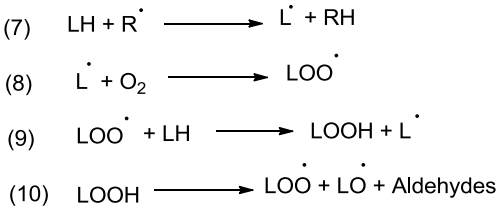
A vast array of molecules are in the human body that more susceptible to free radical attacks than others. These include fats, cellular membranes, DNA, RNA, proteins, carbohydrates and vitamins.

Table 1. Types of the free radicals

Name	Symbol
Hydroxyl radical	•OH
Hydrogen peroxide	H_2O_2
Peroxyl radical	ROO•
Lipid hydroperoxide	LOO•
Singlet oxygen	$^1O_2$
Superoxide ion	$O_2^{\bullet-}$
Nitric oxide	NO•
Peroxynitrite	$ONOO^-$

Reaction of hydroxyl radical with guanine and the sugar moiety of DNA are shown in Scheme 1 and 2 (10).

Lipid peroxidation is important in vivo and has been widely associated with the tissue injuries and diseases (11). The mechanism of lipid peroxidation is shown in Eq. 7-10. Generally lipid hydroperoxides are broken down to aldehydes. Commonly aldehydes are biologically active compounds, which attack to the other parts of the cell (12,13).



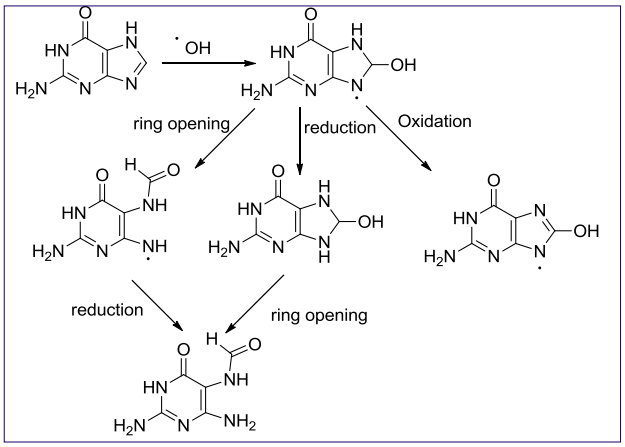
Antioxidants: free radical scavengers

The concept of biological antioxidant relation to any compound that, when existing at a lower concentration compared to that of an oxidizable substrate, is able to either delay or prevent the oxidation of the substrate (14). Antioxidant roles include DNA mutations, lowering OS, malignant transformations, as well as other parameters of cell damage.

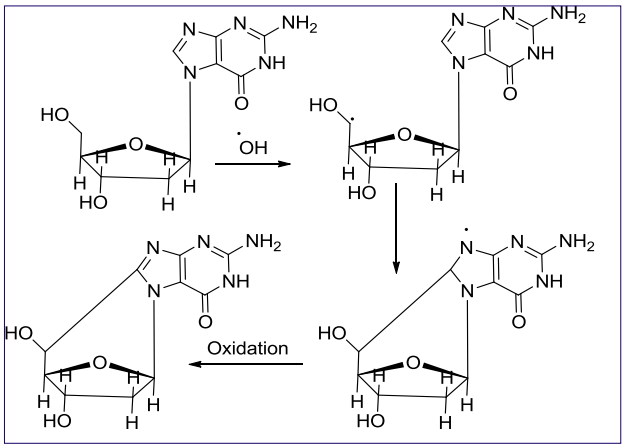
The body has a defense system for prevention of free radical damage. The first identified types of antioxidant defense systems are those that prevent ROS occurrence and those that block or capture the radicals that are formed. Another antioxidant system of the cell is represented by repair processes which remove the damaged biomolecules before their aggregation enables alteration of cell metabolism (15). The repair system intervention consists removing oxidized proteins by proteolytic systems, repairing oxidatively damaged nucleic acids by specific enzymes and repairing oxidized lipids using phospholipases, peroxidases or acyltransferases (16).

Table 2. The Sources free radical formation in the biological system

Sources of free radicals	Mechanism
Transition metal ions	Copper and iron facilitate hydroxyl radical formation
Inflammation	Free radicals released by activated phagocytes
Mitochondrial electron transport	Leakage of superoxide due to inefficient reduction of oxygen
Drug metabolism	Free radical intermediates created during metabolism
Enzymes like xanthine oxidase	Release superoxide during reperfusion of ischemic tissues
Radiation	X-rays and ultraviolet (UV) rays
Cigarette smoking	Gas phase reach in free radicals



Scheme 1. Reaction of hydroxyl radical with guanine.



Scheme 2. Reaction of hydroxyl radical with the sugar moiety of DNA.

Antioxidants include the enzymatic antioxidants and non-enzymatic antioxidants. These two types of antioxidants modulate the free radical reactions. Body protects itself from free radicals via enzymatic antioxidant mechanisms (17). The antioxidant enzymes decrease the levels of lipid hydroperoxide and H_2O_2, therefore they are important in the prevention of lipid peroxidation and keeping the structure and function of cell membranes. Examples of the enzymatic antioxidants are CAT, GSHPx, SOD, and peroxiredoxin (Table 3) (18,19).

The non-enzymatic antioxidants are of two kinds, the natural antioxidants and the synthetic antioxidants that include vitamins (vitamin E, C, A), bioflavonoids, carotenoids, hydroxycinnamates, theaflavin, theaflavin-3-gallate, allicin, piperine and curcumin. In Schemes 3 and 4 the mechanism of radical scavenging activity of vitamin A, allicin and 2-propenesulfenic acid are shown.

Synthetic antioxidants are added to foods that are sensitive to oxidation to prevent oxidative rancidity. Oxidative rancidity results in demolition of vitamins and essential fatty acids, degradation of flavor, and creation of free radicals that cause stress and damage to our bodies. Synthetic antioxidants which have phenolic structure include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and gallic acid esters (23). The antioxidant mechanisms of BHT are shown in Scheme 5.

Oxidative stress and diseases

OS is defined as unbalance between the production of free radicals and the ability of the body to counteract their dangerous effects through neutralization by antioxidants (24). In certain pathological conditions, increased production of ROS and depletion of antioxidants in defense system leads to enhanced ROS activity and OS, resulting tissue damage. OS causes tissue damage by different mechanisms including production of lipid peroxidation, DNA damage, and protein modification. These processes have been related with the pathogenesis of several systemic diseases such as hypertension, diabetes mellitus, and hypercholesterolemia and also kidney disease. In recent years, OS has become one of the most beloved topics in research of molecular mechanism of renal diseases.

Oxidative stress and kidney damage

The kidney is a body part highly vulnerable to damage caused by ROS, likely due to the plenty of long chain polyunsaturated fatty acids in the structure of renal lipids. In recent years, OS has been converted as one of the most popular subjects in research of molecular mechanism of renal disease.

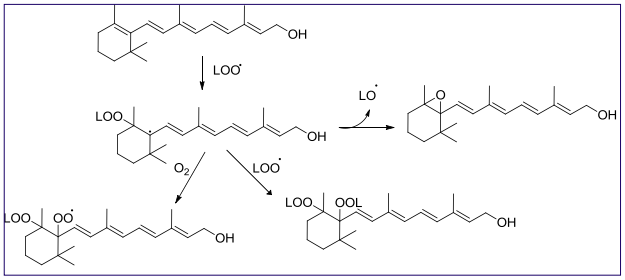
Factors that induce OS in kidney include systemic diseases such as hypertension, diabetes mellitus, hypercholesterolemia, infection, chemotherapeutics, radiocontrast agents environmental toxins, radiation, antibiotics, smoking, occupational chemicals, as well as alcohol consumption. In continuing, we will discuss the relationship between these factors and OS in kidney.

Diabetes mellitus and its association with oxidative stress in kidney

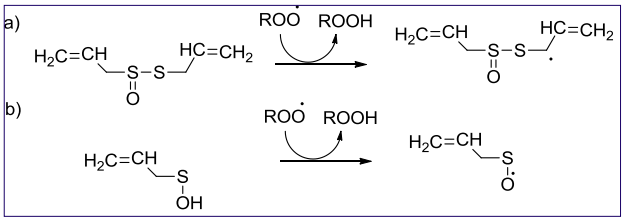
Recent studies have shown that free radicals and kidney damage are associated with diabetic nephropathy. According to this suggestion, diabetes leads to increased glomerular hyperfiltration and a resultant increased glomerular pressure. These lead to damage to glomerular cells and to development of focal and segmental glomerulosclerosis (25,26). Angiotensin II inhibitors decrease glomerular pressure and inhibit albuminuria. Increased angiotensin II

Table 3. Enzymatic antioxidants, their cellular locations and the reactions they carry-out

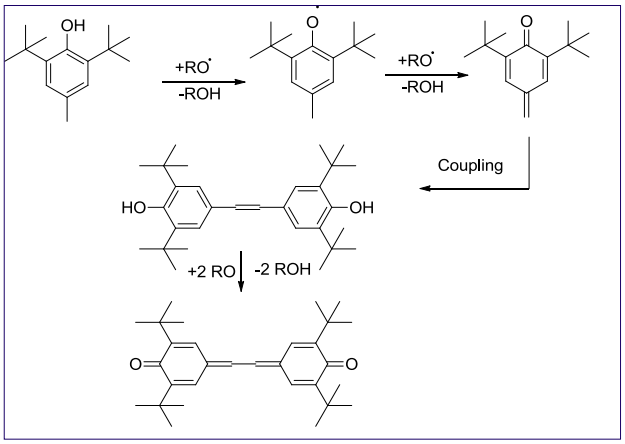
Enzymatic antioxidant	Cellular location	Substrate	Action
GSH	Cytosol	H_2O_2	H_2O_2+GSH→GSSG+ H_2O
CAT	Peroxisomes cytosol	H_2O_2	$2H_2O_2$→ O_2+ H_2O
Prx–I	Cytosol	H_2O_2	H_2O_2+$TrxS_2$→$Trx(Sh)_2$+ H_2O
Mn/Cu/Zn SOD	Mitochondrial matrix (Mn SOD) cytosol (Cu/Zn SOD)	$O_2^{\bullet-}$	$O_2^{\bullet-}$→ H_2O_2



Scheme 3. Mechanism of radical scavenging activity of vitamin A (20).



Scheme 4. Mechanism for the radical-trapping activity of a) allicin (21) and b) 2-propenesulfenic acid (22).



Scheme 5. The antioxidant mechanisms of BHT.

level induces OS through activation of NADPH oxidase, stimulating inflammatory cytokines, and so forth (27,28). Recently, researches have shown that hyperglycemia-induced OS has role in the pathophysiology of diabetic nephropathy. Lipoic acid as antioxidant improves albuminuria and pathology in diabetes by decrease of OS. Lipoic acid has antioxidant potential and the ability of inhibiting lipid peroxidation (29).

Increased blood glucose raises glycosylation of circulator and cellular protein and may incept a series of autoxidation reactions that culminate in the production and accumulation of advanced glycosylation end-products (AGEs) in tissues. The AGEs have oxidizing potential and raise tissue damage by oxygen-free radicals (30).

Hypertension, hypercholesterolemia, fatness, and aging associated with oxidative stress in kidney

Hypertension is one of the main reasons of development of renal failure. Basic cause of this pathology is OS. The most common reason of secondary hypertension is renal artery stenosis that may lead to decrease of renal function and ischemic nephropathy. There is a relation between hypoperfusion and atherosclerosis to interactively increased OS, inflammation and tubular injury in the stenotic kidney (31).

High-fat diet-induced obesity leads to increased hepatic, cardiac and renal tissue OS, which is accompanied by reduction in the antioxidant enzymes activities and glutathione levels that have relation with the increase in MDA and protein carbonyl (PCO) levels (32).

Monocyte chemoattractant protein-1 (MCP-1) is a potent stimulator of macrophage recruitment. It is increased in adipose tissue in obesity and in diabetic kidneys, suggesting that inflammation of these tissues may be MCP-1-dependent (33). Thus we can conclude from these results that macrophages are the reason of increased OS and renal injury in diabetes and obesity-induced renal injury.

Aging is linked with increased OS. Aging cause changes in the kidney such as excessive fibrosis. An increase in apoptosis in cells that control healthy renal functions are often related to excess OS (34). At a molecular level, with old increased mutations in nuclear and mitochondrial DNA (mtDNA), increased lipofuscin and AGEs, increased OS, and increased apoptosis have been identified. Proximal tubular cells have large numbers of mitochondria and are the most reliant upon oxidative phosphorylation and most active to oxidant-induced apoptosis and mutations (35). Recent researches have shown that anti-aging gen, klotho, has role in renal aging and OS-induced renal damage.

Urinary obstruction, urolithiasis, infection, ischemia reperfusion injury, transplantation of kidney, are associated with oxidative stress in kidney

Most experimental and clinical researches have shown that OS is increased in kidney and systemic circulation. It has been reported that the actions of catalase and manganese superoxide dismutase were raised in early stage of ethylene glycol-induced urolithiasis model in rats. In this experiment, the probable mechanism that leads to free radical raise in the kidney may be different in the course of ethylene glycol-induced urolithiasis. Primarily systemic circulation may bring the toxic substances to the kidney, and finally these substances lead to generate free radicals. In the late step, progressive accumulation of leukocytes and imperfect antioxidant enzyme activities may cause kidney to remain under huge amount of OS (36,37). In experimental urolithiasis studies have shown that decreased antioxidant enzyme activities and involvement of NFκB and p38-MAPK (mitogen-activated protein kinase) signaling pathways are related to OS in rat kidney (38-41).

Urinary obstruction and ureteral obstruction owing to urolithiasis is a general urological difficulty seen in urology practice. Unilateral ureteral obstruction (UUO) causes decreased renal CAT and MnSOD protein. UUO-induced nephrotoxicity and renal fibrosis lead to increased OS in kidney.

Infection is another agent that induces OS in kidney. There are many experiments showing that increased OS and re-

duced antioxidant defense mechanisms and antioxidant enzyme systems in kidney may be due to infection (42-45). ROS are important mediators that have damaging effects on various organs including kidney during ischemia reperfusion (IR) injury. OS also has a role as a mediator of injury in chronic allograft tubular atrophy and interstitial fibrosis in rat kidney (46).

Renal transplantation is associated with increased OS in kidney in human and animals. Pre-transplant and post-transplant conditions lead to OS increases in transplanted kidney. If there is preexisting diseases such as inflammation, chronic kidney failure, and diabetes mellitus, kidneys are more sensitive to OS during reperfusion injury. Postoperative immunosuppressive agents are among many risk factors of increased OS in kidney (47).

Antineoplastic agents, antibiotics, immunosuppressant drugs, analgesics, nonsteroidal anti-inflammatory drugs, and radiocontrast agents are associated with oxidative stress in kidney

Antineoplastic agents are used for the treatment of metastatic cancers. Excess ROS production and depressed antioxidant defense mechanism are responsible for nephrotoxicity. Cisplatin is the well-known and used antineoplastic and nephrotoxic agent. Other nephrotoxic anticancer agents are carboplatin, methotrexate, doxorubicin, cyclosporine and adriamycin.

Antibiotics are nephrotoxic agents that cause induction of OS and depletion of antioxidant enzyme activities in kidney. Researchers showed the protective effects of antioxidants and reactive oxygen scavenger agents against gentamicin-induced nephrotoxicity (48-50).

Immunosuppressants such as sirolimus and cyclosporine lead to nephrotoxicity via OS (51-60).

Analgesics, particularly paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used throughout the world. Numerous in vitro and in vivo studies showed that analgesics nephrotoxicity is lead to increased ROS in kidney (58-60).

Contrast-induced nephropathy (CIN) that is used in imaging procedures is a main clinical concern. CIN is the third main common cause of acute kidney injury in hospitalized patients (61). Experimental in vitro and vivo researches illustrate raised hypoxia and the formation of ROS inside the kidney following the administration of iodinate contrast media. The use of N-acetyl cysteine and bicarbonate infusion as ROS scavengers lead to reduced ROS in kidney.

Alcohol, smoking, environmental toxins, irradiation and mobile phones associated with oxidative stress in kidney

Ethanol and its metabolites are exorcised into urine, and their amounts in the urine are higher than that of the blood and the liver. Chronic alcohol administration reduces the renal tubular reabsorption and reduces renal function. Functional abnormalities of renal tubules may be related with ethanol-induced changes in membrane composition and lipid peroxidation.

A result of industry is increased air pollution that is another life menacing health problem (62). The effect of the pathological changes of diesel exhaust particles (DEPs) on systolic blood pressure (SBP), systemic inflammation, OS, and morphological alterations in lungs, heart, liver, and kidneys in Wistar rats have been shown. So that DEPs lead to inflammation especially in lungs and pulmonary tissue, and these pathological changes are attributed to increased OS and inflammatory cytokines in these tissues (63). Lead and cadmium nephrotoxicity are also associated with increase OS in kidney (64,65).

Radiation is an important reason of OS, radiation is commonly used for diagnostic and therapeutic purposes. Chronic OS after total body irradiation leads to radiation nephropathy in rats. The effect of extremely low-frequency electromagnetic field (ELF-EMF) with pulse trains exposure on lipid peroxidation has been shown to lead to OS in the rat liver and kidney tissue. The flow cytometric data proposed a possible association between the exposure to magnetic field and the cell death; however, there were significantly lower necrotic cell percentages in experimental animals compared to either unexposed (66). These results showed the inductive effect of radiation on OS in kidney.

For the last two decades, a large number of studies have investigated the effects of mobile phone radiation on the human and animal. Male reproductive system is among the most affected system (67,68). Increased OS plays a main role in radiofrequency-electromagnetic-waves- (RF-EMW) induced tissue damage.

Conclusion

There is many literatures concerning the association between the OS and renal diseases. Systemic diseases such as diabetes mellitus, hypertension, and hypercholesterolemia; antibiotics, infection; radiocontrast agents and chemotherapeutics; and environmental toxins, radiation, occupational chemicals, smoking, as well as alcohol consumption are associated with induction of OS in the kidney. The kidney is a body part highly vulnerable to damage caused by ROS, due to the plenty of long chain polyunsaturated fatty acids in the structure of renal lipids. Antioxidants have been shown to be effective in animals for protecting kidney. Antioxidant may prevent the OS by peroxidation, inhibiting free radicals and also via other mechanism which can inhibit diseases.

Authors' contribution

Primary draft by SH. SSBM and MRT researching the data and conducted primary editing. Editing the final manuscript by MRK.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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